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L5 59 DUP REM L4 (28 DUPLICATES REMOVED)

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L5 ANSWER 1 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 2000:330629 BIOSIS

DOCUMENT NUMBER: PREV200000330629

TITLE: **HER2 extracellular** domain.

AUTHOR(S): Hudziak, Robert Michael (1); Shepard, H. Michael; Ullrich, Axel

CORPORATE SOURCE: (1) San Bruno, CA USA

ASSIGNEE: Genentech, Inc., South San Francisco, CA, USA

PATENT INFORMATION: US 6015567 January 18, 2000

SOURCE: Official Gazette of the United States Patent and Trademark Office Patents, (Jan. 18, 2000) Vol. 1230, No. 3, pp. No pagination. e-file.
ISSN: 0098-1133.

DOCUMENT TYPE: Patent

LANGUAGE: English

AB A method of treating a human patient via active immunotherapy comprising administering an effective amount of **extracellular** portion of human **HER2** receptor to the patient wherein the method provokes a cell-mediated immune response to HER2 receptor in the patient treated therewith.

L5 ANSWER 2 OF 59 MEDLINE

DUPLICATE 1

ACCESSION NUMBER: 2000402357 MEDLINE

DOCUMENT NUMBER: 20374304

TITLE: Prevention of mammary tumors with a chimeric HER-2 B-cell epitope peptide vaccine.

AUTHOR: Dakappagari N K; Douglas D B; Triozzi P L; Stevens V C; Kaumaya P T

CORPORATE SOURCE: College of Biological Sciences, Department of Microbiology,

The Ohio State University, Columbus 43210, USA.

CONTRACT NUMBER: P30 CA 16058 (NCI)

SOURCE: CANCER RESEARCH, (2000 Jul 15) 60 (14) 3782-9.
Journal code: CNF. ISSN: 0008-5472.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 2000
ENTRY WEEK: 2001004

AB Synthetic peptide vaccines targeting B-cell epitopes of the **extracellular** domain of the **HER-2** oncoprotein were evaluated for their capacity to elicit HER-2-specific antibodies with

antiproliferative activity. Several HER-2 B-cell epitopes were identified by computer-aided analysis of protein antigenicity, and selected B-cell epitopes were synthesized colinearly with a promiscuous T-helper epitope (208-302) derived from the measles virus fusion protein at either the NH2 or COOH terminus linked via a four-residue turn sequence (GPSL). In addition, one epitope sequence, 628-647, was mutated to optimize disulfide

pairing to mimic the native HER-2 receptor. All of the four selected epitopes elicited high-titered antibodies in outbred rabbits with exceptionally high titers for MVF-HER-2(628-647). These antibodies were cross-reactive with the native HER-2 receptor. Antibodies elicited by MVF-HER-2(628-647) inhibited proliferation of human HER-2-overexpressing breast cancer cells in vitro and caused their antibody-dependent cell-mediated cytotoxicity. Furthermore, immunization with MVF-HER-2(628-647) prevented the spontaneous development of HER-2/neu-overexpressing mammary tumors in 83% of transgenic mice. The engineered, chimeric peptide B-cell immunogen MVF-HER-2(628-647) may have applications in the prevention of HER-2-overexpressing cancers.

L5 ANSWER 3 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 2000:275569 BIOSIS

DOCUMENT NUMBER: PREV200000275569

TITLE: Scavenging of **extracellular** H2O2 inhibits the proliferation of **HER-2**/Neu-transformed rat fibroblasts through multiple signalling pathways.

AUTHOR(S): Preston, Thomas John (1); Singh, Gurmit

CORPORATE SOURCE: (1) Hamilton Regional Cancer Ctr, McMaster Univ, Hamilton, ON Canada

SOURCE: Proceedings of the American Association for Cancer Research

Annual Meeting, (March, 2000) No. 41, pp. 789. print..
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco,

California,

USA April 01-05, 2000

ISSN: 0197-016X.

DOCUMENT TYPE: Conference

LANGUAGE: English

SUMMARY LANGUAGE: English

L5 ANSWER 4 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 2000:275321 BIOSIS

DOCUMENT NUMBER: PREV200000275321

TITLE: Differential anti-tumor effects of targeting distinct epitopes of the **Her-2**/neu **extracellular** domain in xenograft models of prostate cancer.

AUTHOR(S): Agus, David B. (1); Scher, Howard I.; Fox, William D.; Higgins, Brian; Maiese, Krista M.; Akita, Robert A.; Pisacane, Paul I.; Sliwkowski, Mark X.

CORPORATE SOURCE: (1) Genentech. Inc., South San Francisco, CA USA

SOURCE: Proceedings of the American Association for Cancer Research

Annual Meeting, (March, 2000) No. 41, pp. 719. print..
Meeting Info.: 91st Annual Meeting of the American Association for Cancer Research. San Francisco,

California,

USA April 01-05, 2000

ISSN: 0197-016X.

DOCUMENT TYPE: Conference
LANGUAGE: English
SUMMARY LANGUAGE: English

L5 ANSWER 5 OF 59 MEDLINE
ACCESSION NUMBER: 2000235468 MEDLINE
DOCUMENT NUMBER: 20235468
TITLE: Pathogenesis of Paget's disease: epidermal heregulin-alpha, motility factor, and the HER receptor family.
AUTHOR: Schelfhout V R; Coene E D; Delaey B; Thys S; Page D L; De Potter C R
CORPORATE SOURCE: N. Goormaghtigh Institute for Pathology, University Hospital, Gent, Belgium.
SOURCE: JOURNAL OF THE NATIONAL CANCER INSTITUTE, (2000 Apr 19) 92 (8) 622-8.
Journal code: J9J. ISSN: 0027-8874.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200007
ENTRY WEEK: 20000701

AB BACKGROUND AND METHODS: In Paget's disease of the breast, the epidermis of

the nipple is infiltrated by large neoplastic cells of glandular origin. It has been hypothesized that the spread of Paget cells through the nipple

epidermis is induced by a motility factor that acts via the HER2/NEU receptor. To test this hypothesis, we characterized and purified a motility factor released by keratinocytes and identified its target receptors in specimens from patients with Paget's disease and in SK-BR-3 breast adenocarcinoma cells, which overexpress HER2/NEU. RESULTS: We isolated the motility factor from keratinocyte-conditioned medium and sequenced tryptic peptides. These sequences were used to identify the motility factor as heregulin-alpha, which is released by skin keratinocytes. Heregulin-alpha induces spreading, motility, and chemotaxis

of SK-BR-3 cells, as does motility factor. Motility factor activities of heregulin-alpha are inhibited by monoclonal antibody AB2, directed against

the extracellular domain of HER2/NEU, which blocks the binding of heregulin-alpha. We used in situ hybridization to show that normal epidermal cells produce heregulin-alpha messenger RNA and that heregulin receptors, HER3 and/or HER4, as well as their coreceptor HER2/NEU, are expressed by Paget cells. CONCLUSIONS: Heregulin-alpha is a motility factor that is produced and released by normal epidermal keratinocytes and thus plays a key role in the pathogenesis of Paget's disease. Paget cells express heregulin receptors HER2/NEU, as well as

HER3 and/or HER4, both of which function as a co-receptor of HER2/NEU. Binding of heregulin-alpha to the receptor complex on Paget cells results in the chemotaxis of these breast cancer cells, which eventually migrate into the overlying nipple epidermis.

L5 ANSWER 6 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 2000:373289 BIOSIS
DOCUMENT NUMBER: PREV200000373289
TITLE: Biodistribution and radioimmunotherapy of human breast cancer xenografts with radiometal-labeled DOTA conjugated anti-HER2/neu antibody 4D5.
AUTHOR(S): Tsai, S. W.; Sun, Y. Y.; Williams, L. E.; Raubitschek, A. A.; Wu, A. M.; Shively, J. E. (1)
CORPORATE SOURCE: (1) Division of Immunology, Beckman Research Institute of

SOURCE: the City of Hope, Duarte, CA, 91010
Bioconjugate Chemistry, (May June, 2000) Vol. 11, No. 3,
pp. 327-334. print.
ISSN: 1043-1802.

DOCUMENT TYPE: Article
LANGUAGE: English
SUMMARY LANGUAGE: English

AB HER2/neu oncogene encodes a 185 kDa trans-membrane protein which is overexpressed in 20-30% of breast and ovarian cancers and portends a poor prognosis. We have studied the targeting and therapy of this oncoprotein with 4D5, a murine monoclonal antibody which recognizes a distinct epitope on the **extracellular** domain of **HER2/neu**. We conjugated the antibody with an active ester of the macrocyclic chelating agent DOTA, radiolabeled the conjugate with either 111In or 90Y, and studied the antibody distribution and therapy, respectively, in athymic mice bearing ~~xenografts of MCF7/HER2/neu, a human breast cancer cell line transfected~~ with the HER2/neu oncogene. For the biodistribution of 111In-labeled DOTA-4D5, a high specificity of tumor localization (30% ID/g) was seen with a tumor-to-blood ratio of greater than 2 at 48 h postinjection. Compared to a previously published study with 125I-labeled 4D5 in beige nude mice bearing NIH3T3/HER2/neu xenografts (De Santes et al. (1992) Cancer Res. 52, 1916-1923), 111In-labeled 4D5 antibody gave superior antibody uptake in tumor (30% ID/g vs 17% ID/g at 48h). In the therapy study, treatment of the nude mice bearing MCF7/HER2/neu xenografts with 100 µCi (3 mug) of 90Y-labeled DOTA-4D5 caused a 3-fold reduction of tumor growth compared to untreated controls (injected with human serum albumin) in 40 days. Treatment of animals with 100 µCi of nonspecific antibody 90Y-labeled DOTA-Leu16 (3 mug) had no tumor growth inhibition. Treatment with unlabeled DOTA-4D5 (3 mug) had a slight effect on tumor growth compared to untreated controls. When analyzed at the level of single animals, no effect was seen in seven of nine animals; however, in two of the animals, tumor growth inhibition was observed. Although a cold antibody therapeutic effect was unexpected at this dose level (3 mug), it may be possible that in some animals that 3 mug of antibody of 90Y-labeled DOTA-4D5 augmented tumor growth reduction. To further explore the effects of cold antibody treatment alone, animals were treated with 100 or 400 mug of unlabeled 4D5 administered in two doses. These animals showed a 1.7-1.8-fold reduction in tumor growth over 28 days, a result less than that obtained with RIT only.

L5 ANSWER 7 OF 59 MEDLINE DUPLICATE 3
ACCESSION NUMBER: 2000125829 MEDLINE
DOCUMENT NUMBER: 20125829
TITLE: Automated assay for HER-2/neu in serum.
AUTHOR: Payne R C; Allard J W; Anderson-Mausser L; Humphreys J D; Tenney D Y; Morris D L
CORPORATE SOURCE: Lab Testing Segment, Business Group Diagnostics, Bayer Corporation, Tarrytown, NY 10591, USA.
SOURCE: CLINICAL CHEMISTRY, (2000 Feb) 46 (2) 175-82.
Journal code: DBZ. ISSN: 0009-9147.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 200004
ENTRY WEEK: 20000404
AB BACKGROUND: The **extracellular** domain of the **HER-2/neu** oncogene product is increased in sera of some patients with epithelial cancers. Our aim was to develop an automated serum assay for the **extracellular** domain of the **HER-2/neu** protein. METHODS: We used a monoclonal antibody labeled with fluorescein

for capture and a monoclonal Fab' fragment labeled with alkaline phosphatase for detection. Separation of bound and free detection conjugate was performed with magnetizable particles coated with monoclonal antibody to fluorescein. Alkaline phosphatase activity was measured kinetically at 405 or 450 nm. RESULTS: The assay was linear from 0.1 to 250 microg/L. No hook effect was evident up to 10 000 microg/L.

Within-run imprecision (CV) was 0.8-1.2%, and total imprecision was 1.1-1.7%. Cross-reactivity with human epidermal growth factor receptor, which has extensive homology with **HER-2/neu** extracellular domain, was <0.6%. Human anti-mouse antibodies, heterophilic antibodies, and rheumatoid factor did not interfere, nor did the therapeutic monoclonal antibody Herceptin((R)). In 51 healthy females, the mean value was 9.3 microg/L with a range of 6.4-14.0 microg/L. No reagent lot-to-lot variability was detected over four lots of reagents tested. ~~CONCLUSION: The Bayer Immuno-1(TM) assay for HER-2/neu was~~ precise and resistant to interferences, characteristics that are essential for longitudinal monitoring of cancer patients.

L5 ANSWER 8 OF 59 MEDLINE DUPLICATE 4

ACCESSION NUMBER: 2000090818 MEDLINE

DOCUMENT NUMBER: 20090818

TITLE: Role of HER2 gene overexpression in breast carcinoma.

AUTHOR: Menard S; Tagliabue E; Campiglio M; Pupa S M

CORPORATE SOURCE: Molecular Targeting Unit, Department of Experimental Oncology, Istituto Nazionale Tumori, Milan, Italy..
menard@istitutotumori.mi.it

SOURCE: JOURNAL OF CELLULAR PHYSIOLOGY, (2000 Feb) 182 (2) 150-62.
Ref: 170
Journal code: HNB. ISSN: 0021-9541.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 200003

ENTRY WEEK: 20000305

AB The HER2 proto-oncogene encodes a transmembrane glycoprotein of 185 kDa (p185(HER2)) with intrinsic tyrosine kinase activity. Amplification of the HER2 gene and overexpression of its product induce cell transformation. Numerous studies have demonstrated the prognostic relevance of p185(HER2), which is overexpressed in 10% to 40% of human breast tumors. Recent data suggest that p185(HER2) is a ligand orphan receptor that amplifies the signal provided by other receptors of the HER family by heterodimerizing with them. Ligand-dependent activation of HER1, HER3, and HER4 by EGF or heregulin results in heterodimerization and, thereby, HER2 activation. HER2 overexpression is associated with breast cancer patient responsiveness to doxorubicin, to cyclophosphamide, methotrexate, and fluorouracil (CMF), and to paclitaxel, whereas tamoxifen was found to be ineffective and even detrimental in patients with HER2-positive tumors.

In vitro analyses have shown that the role of HER2 overexpression in determining the sensitivity of cancer cells to drugs is complex, and molecules involved in its signaling pathway are probably the actual protagonists of the sensitivity to drugs. The association of **HER2** overexpression with human tumors, its **extracellular** accessibility, as well as its involvement in tumor aggressiveness are all factors that make this receptor an appropriate target for tumor-specific therapies. A number of approaches are being investigated as possible

therapeutic strategies that target HER2: (1) growth inhibitory antibodies, which can be used alone or in combination with standard chemotherapeutics; (2) tyrosine kinase inhibitors (TKI), which have been developed in an effort to block receptor activity because phosphorylation is the key event leading to activation and initiation of the signaling pathway; and (3) active immunotherapy, because the HER2 oncoprotein is immunogenic in some breast carcinoma patients. Copyright 2000 Wiley-Liss, Inc.

L5 ANSWER 9 OF 59 MEDLINE
ACCESSION NUMBER: 1999316773 MEDLINE
DOCUMENT NUMBER: 99316773
TITLE: Generation of immunity to the HER-2/neu oncogenic protein in patients with breast and ovarian cancer using a peptide-based vaccine.
AUTHOR: ~~Disis M L; Grabstein K H; Sleath P R; Cheever M A~~
CORPORATE SOURCE: Division of Oncology, University of Washington, Seattle 98195-6527, USA.. ndisis@u.washington.edu
CONTRACT NUMBER: K08 CA61834 (NCI)
R01 CA75163 (NCI)
M01-RR-00037 (NCRR)
SOURCE: CLINICAL CANCER RESEARCH, (1999 Jun) 5 (6) 1289-97.
Journal code: C2H. ISSN: 1078-0432.
PUB. COUNTRY: United States
(CLINICAL TRIAL)
(CLINICAL TRIAL, PHASE I)
Journal; Article; (JOURNAL ARTICLE)
(RANDOMIZED CONTROLLED TRIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199912
AB HER-2/neu is a "self" tumor antigen that is overexpressed in 15-30% of human adenocarcinomas. Vaccine strategies directed against HER-2/neu and other self tumor antigens require development of methods to overcome immune tolerance to self-proteins. In rats, rat neu peptide vaccines have been shown to be an effective way of circumventing tolerance to rat neu protein and generating rat neu-specific immunity. The present report validates that a similar peptide-based vaccine formulation is effective for inducing T-cell immunity to HER-2/neu protein in humans with breast and ovarian cancer. The vaccine formulation included groups of peptides derived from the HER-2/neu extracellular domain (ECD) or intracellular domain (ICD) mixed with granulocyte macrophage colony stimulating factor as an adjuvant. These peptides were 15-18 amino acids in length and designed to elicit a CD4 T helper-specific immune response. Patients underwent intradermal immunization once a month for a total of two to six immunizations. To date, all of the patients immunized with HER-2/neu peptides developed HER-2/neu peptide-specific T-cell responses. The majority of patients (six of eight) also developed HER-2/neu protein-specific responses. Responses to HER-2/neu protein occurred with epitope spreading. Immune T cells elicited by vaccination were shown to migrate outside the peripheral circulation by virtue of generating delayed type hypersensitivity responses distant from the vaccine site, which indicated the potential ability to traffic to the site of tumor. The use of peptide-based vaccines may be a simple, yet effective, vaccine strategy for immunizing humans to oncogenic self-proteins.

L5 ANSWER 10 OF 59 MEDLINE
ACCESSION NUMBER: 1999352341 MEDLINE
DOCUMENT NUMBER: 99352341
TITLE: Relative cytotoxic activity of immunotoxins reactive with

DUPLICATE 5

different epitopes on the extracellular domain of the
erbB-2 (HER-2/neu) gene product, p185.

AUTHOR: Boyer C M; Pusztai L; Wiener J R; Xu F J; Dean G S; Bast B
S; O'Brian K C; Greenwald M; DeSombre K A; Bast R C Jr
CORPORATE SOURCE: Department of Medicine, Duke University Medical Center,
Durham, NC, USA.
CONTRACT NUMBER: CA 39930 (NCI)
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1999 Aug 12) 82 (4)
525-31.
Journal code: GQU. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals.
ENTRY MONTH: 199910

AB Different epitopes on the **extracellular** domain of the
HER-2 receptor can serve as distinct targets for
immunotoxins. To determine the optimal epitope target for immunotoxin
therapy, 7 anti-HER-2 ricin A chain murine monoclonal immunotoxins, each
reactive with different epitopes of HER-2 receptor, were tested for
cytotoxic activity. The immunotoxins produced 1.2-4.6 logs of
cytotoxicity
in limiting dilution clonogenic assays with 2 breast cancer cell lines
that overexpressed HER-2. Cytotoxicity did not correlate with
immunoglobulin isotype, binding affinity, relative position of epitopes
or
internalization of the anti-HER-2 immunotoxins. Interestingly, the most
and least effective immunotoxins bound to epitopes in very close
proximity. Competitive binding assays with unconjugated antibodies have
previously indicated that our antibodies recognized epitopes that are
arranged in a linear array. To orient this relative epitope map,
deletions
were prepared in the HER-2/neu gene and these mutant constructs were
expressed in NIH3T3 cells. Epitope expression was determined by antibody
binding and radioimmunoassay. Epitopes targeted by the PB3, 454C11 and
NB3
antibodies are localized N-terminal to the epitopes recognized by ID5,
BD5, 741F8 and 520C9 antibodies. The 2 non-conformational epitopes PB3
and
NB3 were localized to regions corresponding to amino acids 78-242 of the
p185(HER-2) protein. Copyright 1999 Wiley-Liss, Inc.

L5 ANSWER 11 OF 59 MEDLINE DUPLICATE 6
ACCESSION NUMBER: 1999376336 MEDLINE
DOCUMENT NUMBER: 99376336
TITLE: Isolation and characterization of an anti-CD16
single-chain
Fv fragment and construction of an anti-HER2/neu/anti-CD16
bispecific scFv that triggers CD16-dependent tumor
cytolysis.
AUTHOR: McCall A M; Adams G P; Amoroso A R; Nielsen U B; Zhang L;
Horak E; Simmons H; Schier R; Marks J D; Weiner L M
CORPORATE SOURCE: Fox Chase Cancer Center, Philadelphia, PA 19111, USA.
CONTRACT NUMBER: CA65559 (NCI)
CA06927 (NCI)
CA50633 (NCI)
SOURCE: MOLECULAR IMMUNOLOGY, (1999 May) 36 (7) 433-45.
Journal code: NG1. ISSN: 0161-5890.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199910
AB Bispecific antibody (bsAb)-based clinical trials of cancer have been
conducted primarily using intact murine monoclonal antibody (mAb)-derived

molecules. In some of these trials, toxicity resulting from the interactions of antibody Fc domains with cellular Fc receptors has limited the doses of antibody (Ab) that can be employed. Furthermore, human anti-mouse Ab responses prohibit multiple therapy courses. These factors have decreased the efficacy of the bsAb 2B1, which targets the extracellular domains (ECD) of the HER2/neu protooncogene product and the human FcγRIII (CD16). To address these obstacles, we have constructed and characterized a fully human gene-fused bsAb from single-chain Fv (scFv) molecules specific for HER2/neu and CD16.

The human anti-CD16 scFv component, NM3E2, was isolated from a human scFv phage display library. As binding of NM3E2 to human neutrophil-associated CD16 decreased in the presence of plasma IgG, we have concluded that NM3E2 recognizes an epitope in the vicinity of the Fc binding pocket. Furthermore, the NM3E2 scFv was found by surface plasmon resonance-based epitope mapping to share an overlapping epitope with the Leu-11c mAb. The human anti-HER2/neu scFv component, C6.5, which was previously isolated from a human scFv phage display library, was employed as fusion partner for the creation of a bispecific scFv (bs-scFv). In the presence of the C6.5 x NM3E2 bs-scFv, peripheral blood lymphocytes promoted significant lysis of human SK-OV-3 ovarian cancer cells overexpressing HER2/neu. Biodistribution studies performed in SK-OV-3 tumor-bearing scid mice revealed that 1% ID/g of 125I-labeled C6.5 x NM3E2 bs-scFv was specifically retained in tumor at 23 h following injection. These results indicated that both scFv components of the bs-scFv retained their function in the fusion protein. This bsAb should overcome some of the problems associated with the 2B1 bsAb. C6.5 x NM3E2 bs-scFv offers promise as a platform for multifunctional binding proteins with potential clinical applications as a result of its human origin, lack of an Fc domain, ease of production, high level of in vitro tumor cell cytotoxicity and highly selective tumor targeting.

L5 ANSWER 12 OF 59 MEDLINE

DUPLICATE 7

ACCESSION NUMBER: 1999398161 MEDLINE

DOCUMENT NUMBER: 99398161

TITLE: Expression of C-erbB-2/HER-2 in patients with metastatic breast cancer undergoing high-dose chemotherapy and autologous blood stem cell support.

AUTHOR: Bewick M; Chadderton T; Conlon M; Lafrenie R; Morris D; Stewart D; Gluck S

CORPORATE SOURCE: Northeastern Ontario Regional Cancer Centre, Sudbury, Ontario, Canada.

SOURCE: BONE MARROW TRANSPLANTATION, (1999 Aug) 24 (4) 377-84. Journal code: BON. ISSN: 0268-3369.

PUB. COUNTRY: ENGLAND: United Kingdom Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199912

AB C-erbB-2/HER-2 (designated HER-2) is overexpressed in both primary and metastatic breast cancer and predicts poor prognosis. We investigated the expression of HER-2 in patients with metastatic breast cancer undergoing high-dose chemotherapy (HDCT) with autologous blood stem cell (ABSC) support and correlated the presence (positive) or absence (negative) of HER-2 overexpression in these patients with response to treatment, progression-free survival (PFS) and overall survival (OS). The level of HER-2 expression was analyzed in 57 patients with metastatic breast

cancer undergoing HDCT with ABSC support. Plasma from peripheral blood was taken at three different time points during the course of treatment and was analyzed using an enzyme immunoassay (EIA) to detect circulating levels of

the extracellular portion of HER-2.

HER-2 levels were elevated (>0.2 U/mg protein) 27/57

(47.4%) patients at one or more time points during treatment. The level

of

HER-2 varied during the course of treatment. Following induction chemotherapy (ICT), five patients who were negative initially, showed overexpression of HER-2. Three patients overexpressed HER-2 only after HDCT/ABSC. Response to treatment was similar in patients independent of plasma HER-2 levels. Overexpression of HER-2 was associated with a significantly shorter PFS (P = 0.004, log rank) and OS (P = 0.003, log rank) after HDCT/ABSC. HER-2 overexpression, patient age, estrogen receptor status, progesterone receptor status, and previous hormone treatment were assessed by univariate and multivariate analysis. Univariate analysis determined that only HER-2 overexpression correlated significantly with decreases in progression free survival (P = 0.005, Cox regression). Decreased overall survival correlated significantly with HER-2 overexpression (P = 0.004) and decreased expression of both

estrogen

receptor (P = 0.032) and progesterone receptor (P = 0.039). In multivariate analysis of these variables, only HER-2 expression levels proved to be of independent statistical significance in predicting

outcome

for both PFS (P = 0.007) and OS (P = 0.002). These results suggest that overexpression of HER-2, measured by EIA in plasma may predict a shorter PFS and OS in patients with metastatic breast cancer treated with HDCT

and

ABSC support.

L5 ANSWER 13 OF 59 MEDLINE

DUPLICATE 8

ACCESSION NUMBER: 1999226516 MEDLINE

DOCUMENT NUMBER: 99226516

TITLE: Trastuzumab, a recombinant DNA-derived humanized monoclonal

antibody, a novel agent for the treatment of metastatic breast cancer.

AUTHOR: Goldenberg M M

CORPORATE SOURCE: Mount Sinai NYU Health, New York, New York 10029, USA.

SOURCE: CLINICAL THERAPEUTICS, (1999 Feb) 21 (2) 309-18. Ref: 28
Journal code: CPE. ISSN: 0149-2918.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199907

AB Amplification of the human epidermal growth factor receptor 2 protein (HER2) in primary breast carcinomas has been shown to correlate with poor clinical prognosis for certain patients. Trastuzumab (Herceptin, Genentech, Inc., South San Francisco, California) is a highly purified recombinant DNA-derived humanized monoclonal immunoglobulin G1 kappa antibody that binds with high affinity and specificity to the extracellular domain of the HER2 receptor. In vitro and in vivo preclinical studies have shown that administration of trastuzumab alone or in combination with paclitaxel or carboplatin significantly inhibits the growth of breast tumor-derived cell lines that overexpress the HER2 gene product. At therapeutic doses in breast cancer patients,

the

mean half-life of trastuzumab is 5.8 days. Trastuzumab serum concentrations reach steady state with mean trough and peak

concentrations

of 79 microg/mL and 123 microg/mL, respectively. In a 222-patient, single-arm clinical study, treatment with a loading dose of trastuzumab 4 mg/kg administered IV followed by weekly IV doses of 2 mg/kg produced an overall response rate of 14% (2% complete remission and 12% partial

remission). The beneficial effects were greatest in patients with the greatest degree (3+) of HER2 protein overexpression. In another clinical study, 469 women with metastatic breast carcinoma were randomized to a paclitaxel or anthracycline-plus-cyclophosphamide regimen with or without trastuzumab. The overall response rate was significantly greater in the trastuzumab-plus-chemotherapy group than in the chemotherapy-alone cohort.

The magnitude of observed effects was greatest with paclitaxel plus trastuzumab. The most common adverse effects attributed to trastuzumab in clinical studies were fever and chills, pain, asthenia, nausea, vomiting, increased cough, diarrhea, headache, dyspnea, infection, rhinitis, and insomnia. Trastuzumab in combination with chemotherapy can lead to cardiotoxicity, leukopenia, anemia, (diarrhea, abdominal pain, and infection. Trastuzumab has been approved by the US Food and Drug Administration as a single agent for the treatment of patients who have metastatic breast cancer involving overexpression of the HER2 protein and who have received 1 or more chemotherapy regimens; in combination with paclitaxel, it has been approved for the treatment of such patients who have not received chemotherapy.

L5 ANSWER 14 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 2000:69853 BIOSIS

DOCUMENT NUMBER: PREV200000069853

TITLE: Clinical use of serum c-erbB-2 in patients with ovarian masses.

AUTHOR(S): Cheung, T. H. (1); Wong, Y. F.; Chung, T. K. H.; Maimonis, P.; Chang, A. M. Z.

CORPORATE SOURCE: (1) Department of Obstetrics and Gynaecology, Prince of Wales Hospital, Shatin, New Territories, Hong Kong China

SOURCE: Gynecologic and Obstetric Investigation, (Aug., 1999) Vol. 48, No. 2, pp. 133-137.
ISSN: 0378-7346.

DOCUMENT TYPE: Article

LANGUAGE: English

SUMMARY LANGUAGE: English

AB The c-erbB-2 (Her-2/neu) gene product has a large extracellular domain (ECD) and part of which could be identified in the serum. We measured the serum level of c-erbB-2 ECD in 93 patients, who presented with ovarian masses, with an enzyme immunoassay test and an elevated level was found

in 5.5, 16.7 and 38% of patients with benign, borderline and malignant ovarian neoplasms, respectively. This serum marker may reflect the overexpression of c-erbB-2 gene in tumor tissues, which is associated

with poor prognosis. However, measurement of c-erbB-2 ECD when used alone or in combination with CA 125 is not useful in differentiating benign from malignant ovarian tumors.

L5 ANSWER 15 OF 59 MEDLINE

ACCESSION NUMBER: 1999409921 MEDLINE

DOCUMENT NUMBER: 99409921

TITLE: Nonclinical studies addressing the mechanism of action of trastuzumab (Herceptin).

AUTHOR: Sliwkowski M X; Lofgren J A; Lewis G D; Hotaling T E; Fendly B M; Fox J A

CORPORATE SOURCE: Department of Molecular Oncology, Genentech, Inc., South San Francisco, CA 94080, USA.

SOURCE: SEMINARS IN ONCOLOGY, (1999 Aug) 26 (4 Suppl 12) 60-70.
Ref: 75

Journal code: UN5. ISSN: 0093-7754.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199911
AB HER2 is a ligand-less member of the human epidermal growth factor receptor

or ErbB family of tyrosine kinases. In normal biological systems, HER2 functions as a co-receptor for a multitude of epidermal growth factor-like

ligands that bind and activate other HER family members. HER2 overexpression is observed in a number of human adenocarcinomas and results in constitutive HER2 activation. Specific targeting of these tumors can be accomplished with antibodies directed against the extracellular domain of the HER2 protein. One of these antibodies, 4D5, has been fully humanized and is termed trastuzumab (Herceptin; Genentech, San Francisco, CA). Treatment of HER2-overexpressing breast cancer cell lines with trastuzumab results in induction of p27KIP1 and the Rb-related protein, p130, which in turn significantly reduces the number of cells undergoing S-phase. A number of other phenotypic changes are observed in vitro as a consequence of trastuzumab binding to HER2-overexpressing cells. These phenotypic

changes include downmodulation of the HER2 receptor, inhibition of tumor cell growth, reversed cytokine resistance, restored E-cadherin expression levels, and reduced vascular endothelial growth factor production. Interaction of trastuzumab with the human immune system via its human immunoglobulin G1 Fc domain may potentiate its antitumor activities. In vitro studies demonstrate that trastuzumab is very effective in mediating antibody-dependent cell-mediated cytotoxicity against HER2-overexpressing tumor targets. Trastuzumab treatment of mouse xenograft models results in marked suppression of tumor growth. When given in combination with standard cytotoxic chemotherapeutic agents, trastuzumab treatment generally results in statistically superior antitumor efficacy compared with either agent given alone. Taken together, these studies suggest that the mechanism of action of trastuzumab includes antagonizing the constitutive growth-signaling properties of the HER2 system, enlisting immune cells to attack and kill the tumor target, and augmenting chemotherapy-induced cytotoxicity.

L5 ANSWER 16 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1999:390196 BIOSIS

DOCUMENT NUMBER: PREV199900390196

TITLE: Correlation of circulating HER-2/neu extracellular domain with clinical outcome in patients with metastatic breast cancer.

AUTHOR(S): Sledge, George W. (1)

CORPORATE SOURCE: (1) Indiana University Hospital, Indianapolis, IN USA

SOURCE: Seminars in Oncology, (Feb., 1999) Vol. 26, No. 1 SUPPL. 2,

pp. 33.

Meeting Info.: The Fox Chase Cancer Center and Free University Hospital Investigators Workshop and Consensus Conference on Paclitaxel St. Thomas, Virgin Islands, USA March 25-29, 1998 Fox Chase Cancer Center . ISSN: 0093-7754.

DOCUMENT TYPE: Conference

LANGUAGE: English

L5 ANSWER 17 OF 59 MEDLINE

ACCESSION NUMBER: 1999409916 MEDLINE

DOCUMENT NUMBER: 99409916

TITLE: Recent developments in breast cancer therapy.

AUTHOR: Hortobagyi G N; Hung M C; Buzdar A U

CORPORATE SOURCE: Department of Breast Medical Oncology, The University of Texas M.D. Anderson Cancer Center, Houston 77030, USA.

SOURCE: SEMINARS IN ONCOLOGY, (1999 Aug) 26 (4 Suppl 12) 11-20.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199911
ENTRY WEEK: 19991105

AB Over the past three decades conceptual approaches to breast cancer have led to improvements in locoregional therapy and early diagnosis. Systematic screening programs with mammography reduce disease-specific mortality by 25% to 30%, while many patients with early breast cancer receive optimal breast-conserving treatments. Our increased understanding of the biology of breast cancer helped develop successful adjuvant systemic therapies (cytotoxic and hormonal) that, in turn, reduce ~~mortality by 15% to 25%. Newer therapeutic interventions are under~~ intensive investigation. While continued progress in cytotoxic therapy is evident (taxanes, vinorelbine, gemcitabine, new antifolates, liposomal anthracyclines, etc), there is increasing interest in targeting growth factors and their receptors. Thus, a monoclonal antibody directed to the **extracellular** domain of the **HER-2/neu** oncoprotein was recently approved by the Food Drug Administration based

on

evidence of antitumor activity as a single agent and in combination with cytotoxic therapy. A similar approach against the epidermal growth factor receptor is under evaluation in clinical trials. Various methods of inhibiting intracellular signal transduction also are in clinical development. These include tyrosine kinase inhibition, dominant negative mutant inhibitors of GRB-2, farnesyl transferase inhibition and vaccines directed against various epitopes expressed by mammary cancer cells. Angiogenesis and the enzyme telomerase are other targets under intense scrutiny since they are integrally involved with metastases and cellular immortality, both common characteristics of the malignant cell. These lines of investigation are likely to provide innovative therapeutic interventions, which may improve the specificity and therapeutic index of anticancer treatments.

L5 ANSWER 18 OF 59 MEDLINE

DUPLICATE 9

ACCESSION NUMBER: 1999027593 MEDLINE

DOCUMENT NUMBER: 99027593

TITLE: Remission of human breast cancer xenografts on therapy with

humanized monoclonal antibody to HER-2 receptor and DNA-reactive drugs.

AUTHOR: Pietras R J; Pegram M D; Finn R S; Maneval D A; Slamon D J

CORPORATE SOURCE: Department of Medicine, UCLA School of Medicine, Los Angeles, California 90095, USA.

CONTRACT NUMBER: R01-CA60835 (NCI)

R01-CA36827 (NCI)

P01-CA32737 (NCI)

SOURCE: ONCOGENE, (1998 Oct 29) 17 (17) 2235-49.

Journal code: ONC. ISSN: 0950-9232.

PUB. COUNTRY: ENGLAND: United Kingdom

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199901

AB HER-2 oncogene encodes a transmembrane growth factor receptor that is overexpressed in 25-30% of patients with primary breast and ovarian cancer. A murine monoclonal antibody, 4D5, to the **extracellular** domain of **HER-2** receptor elicits cytostatic growth inhibition of tumor cells overexpressing HER-2 protein, but clinical use of this antibody is limited by genesis of human anti-mouse antibodies. To

avoid this problem, a recombinant humanized 4D5 monoclonal antibody (rhuMab HER-2) was developed and tested using a human tumor xenograft model. Human breast and ovarian cancer cells which overexpress HER-2 were inhibited in vivo by the rhuMab HER-2 antibody. Tumor growth relative to control was reduced at all doses of antibody tested, and the magnitude of growth inhibition was directly related to dose of rhuMab HER-2. Tumor growth resumed on termination of antibody therapy, indicating a

cytostatic

effect. To elicit a cytotoxic response, human breast tumor xenografts were

treated with a combination of antibody and antitumor drugs, cisplatin or doxorubicin. The combination of antibody with either cisplatin or doxorubicin resulted in significantly greater growth inhibition, with the cisplatin combination demonstrating a greater response. In addition, therapy with cisplatin and antireceptor antibody elicited complete tumor remissions after 2-3 cycles of therapy. The schedule of administration of anti-receptor antibody and cisplatin was critical for occurrence of ~~antibody-induced potentiation in cisplatin cytotoxicity. Enhanced killing~~ of tumor cells was found only if antibody and drug were given in close temporal proximity. Since interference with DNA repair pathways may contribute to this receptor-enhanced chemosensitivity, repair of cisplatin-damaged reporter DNA (pCMV-beta) was determined in human breast cells. As in studies of antibody-enhanced cisplatin cytotoxicity in vivo, treatment with rhuMab HER-2 blocked the repair of cisplatin-damaged DNA only if the antibody was administered in close temporal proximity to transfection of the drug-exposed reporter DNA. An alternative measure of DNA repair, unscheduled DNA synthesis, was also assessed. Treatment with either cisplatin or doxorubicin led to an increase in unscheduled DNA synthesis that was reduced by combined therapy with antireceptor antibody specific to HER-2-overexpressing breast cancer cells. Using a direct measure of DNA repair, therapy of HER-2-overexpressing cells with rhuMab HER-2 also blocked the removal of cisplatin-induced DNA adducts. Expression of p21/WAF1, an important mediator of DNA repair, was

disrupted

in breast cancer cells with HER-2 overexpression, but not in control cells, after treatment with HER-2 antibody, thus suggesting cross-communication between the HER-2 signaling and DNA repair pathways. These data demonstrate an in vivo antiproliferative effect of rhuMab

HER-2

on tumors that overexpress HER-2 receptor and a therapeutic advantage in the administration of the antireceptor antibody in combination with chemotherapeutic agents.

L5 ANSWER 19 OF 59 MEDLINE

DUPLICATE 10

ACCESSION NUMBER: 1998314863 MEDLINE

DOCUMENT NUMBER: 98314863

TITLE: Prolonged in vivo tumour retention of a human diabody targeting the **extracellular** domain of human HER2/neu.

AUTHOR: Adams G P; Schier R; McCall A M; Crawford R S; Wolf E J; Weiner L M; Marks J D

CORPORATE SOURCE: Department of Medical Oncology, Fox Chase Cancer Center, Philadelphia, PA 19111, USA.

CONTRACT NUMBER: CA 65559 (NCI)
CA06927 (NCI)

SOURCE: BRITISH JOURNAL OF CANCER, (1998 May) 77 (9) 1405-12.
Journal code: AV4. ISSN: 0007-0920.

PUB. COUNTRY: SCOTLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199809

AB Single-chain Fv (scFv) molecules exhibit highly specific tumour-targeting properties in tumour-bearing mice. However, because of their smaller size and monovalent binding, the quantities of radiolabelled scFv retained in

tumours limit their therapeutic applications. Diabodies are dimeric antibody-based molecules composed of two non-covalently associated scFv that bind to antigen in a divalent manner. In vitro, diabodies produced from the anti-HER2/neu (c-erbB-2) scFv C6.5 displayed approximately 40-fold greater affinity for HER2/neu by surface plasmon resonance biosensor measurements and significantly prolonged association with antigen on the surface of SK-OV-3 cells (t_{1/2} cell surface retention of > 5 h vs 5 min) compared with C6.5 scFv. In SK-OV-3 tumour-bearing scid mice, radioiodinated C6.5 diabody displayed a highly favourable balance of quantitative tumour retention and specificity. By as early as 4 h after i.v. administration, significantly more diabody was retained in tumour (10 %ID g(-1)) than in blood (6.7 %ID ml(-1)) or normal tissue (liver, 2.8 %ID g(-1); lung, 7.1 %ID g(-1); kidney, 5.2 %ID g(-1)). Over the next 20 h, the quantity present in blood and most tissues dropped approximately tenfold, while the tumour retained 6.5 %ID g(-1) or about two-thirds of its 4-h value. In contrast, the 24-h tumour retention of radioiodinated C6.5 scFv monomer was only 1 %ID g(-1). When diabody retentions were examined over the course of a 72-h study and cumulative area under the curve (AUC) values were determined, the resulting tumor-organ AUC ratios were found to be superior to those previously reported for other monovalent or divalent scFv molecules. In conclusion, the diabody format provides the C6.5 molecule with a distinct in vitro and in vivo targeting advantage and has promise as a delivery vehicle for therapeutic agents.

L5 ANSWER 20 OF 59 MEDLINE

ACCESSION NUMBER: 1998244897 MEDLINE

DOCUMENT NUMBER: 98244897

TITLE: Role of cross-linking agents in determining the biochemical and pharmacokinetic properties of Mgr6-clavin

immunotoxins.

AUTHOR: Dosio F; Arpicco S; Adobati E; Canevari S; Brusa P; De Santis R; Parente D; Pignanelli P; Negri D R; Colnaghi M I;

Cattel L
CORPORATE SOURCE: Dipartimento di Scienza e Tecnologia del Farmaco, University of Torino, Italy.. dosio@pharm.unito.it
SOURCE: BIOCONJUGATE CHEMISTRY, (1998 May-Jun) 9 (3) 372-81.
Journal code: ALT. ISSN: 1043-1802.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199809
ENTRY WEEK: 19980901

AB Several immunotoxins (ITs) were synthesized by the attachment of clavin, a

recombinant toxic protein derived from *Aspergillus clavatus*, to the monoclonal antibody Mgr6 that recognizes an epitope of the gp185(HER-2) extracellular domain expressed on breast and ovarian carcinoma cells. Conjugation and purification parameters were analyzed in an effort to optimize the antitumor activity and stability of the ITs in vivo. To modulate the in vitro and in vivo properties of the immunotoxins, different coupling procedures were used and both disulfide and thioether linkages were obtained. Unhindered and hindered disulfide with a methyl group linkage ethyl S-acetyl 3-mercaptopropionthioimide ester hydrochloride (AMPT) or ethyl S-acetyl 3-mercaptoputylthioimide ester hydrochloride (M-AMPT) were obtained by reaction with recombinant clavin, while the monoclonal antibody Mgr6 was derivatized with ethyl 3-[(4-carboxamidophenyl)dithio]propionthioimide ester hydrochloride (CDPT). To achieve higher hindrance (a disulfide bond with a geminal dimethyl group), Mgr6 was derivatized with the

N-hydroxysuccinimidyl 3-methyl-3-(acetylthio)butyrate (SAMBA) and clavin with CDPT. To evaluate the relevance of the disulfide bond in the potency and pharmacokinetic behavior of the ITs, a conjugate consisting of a stable thioether bond was also prepared by derivatizing Mgr6 with the N-hydroxysuccinimidyl ester of iodoacetic acid (SIA) and clavin with

AMPT.

The immunotoxins were purified and characterized using a single-step chromatographic procedure. Specificity and cytotoxicity were assayed on target and unrelated cell lines. The data indicate that the introduction of a hindered disulfide linkage into ITs has little or no effect on antitumor activity and suggest that disulfide cleavage is essential for activity; indeed, the intracellularly unbreakable thioether linkage produced an inactive IT. Analysis of IT stability in vitro showed that

the

release of mAb by incubation with glutathione is proportional to the presence of methyl groups and increases exponentially with the increase

in

steric hindrance. Analysis of the pharmacokinetic behavior of ITs in Balb/c mice given intravenous bolus injections indicated that ITs with higher in vitro stability were eliminated more slowly; i.e., the

disulfide

bearing a methyl group doubled the beta-phase half-life (from 3.5 to 7.1 h) compared with that of the unhindered, while a geminal dimethyl protection increased the elimination phase to 24 h. The thioether linkage showed its intrinsic stability with a beta-phase half-life of 46 h. The thioether linkage also increased the distribution phase from 17 to 32

min.

The in vitro characteristics and in vivo stability of Mgr6-clavin conjugates composed of a methyl and dimethyl steric hindered disulfide suggest clinical usefulness.

L5 ANSWER 21 OF 59 MEDLINE

DUPLICATE 11

ACCESSION NUMBER: 1999163969 MEDLINE

DOCUMENT NUMBER: 99163969

TITLE: Circulating tumor markers in breast cancer: accepted utilities and novel prospects.

AUTHOR: Stearns V; Yamauchi H; Hayes D F

CORPORATE SOURCE: Breast Cancer Program, Lombardi Cancer Center, Georgetown University Medical Center, Washington, DC 20007, USA.

SOURCE: BREAST CANCER RESEARCH AND TREATMENT, (1998) 52 (1-3) 239-59. Ref: 112

Journal code: A8X. ISSN: 0167-6806.

PUB. COUNTRY: Netherlands

Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199907

AB Detecting and/or monitoring changes in circulating tumor markers might assist in evaluating cancer risk, diagnosis, prognosis, or response to treatment. Several categories of circulating tumor markers have been investigated in breast cancer. These categories include classical tumor-associated antigens, such as CEA and CA 15-3, markers of tumor biology, including markers of angiogenesis, adhesion, and invasion, and antibody response to tumor-associated antigens such as HER2/neu and p53. We used a recently proposed Tumor Marker Utility Grading System to evaluate the use of several circulating tumor markers for different clinical utilities in breast cancer. While there are no tumor markers

with

established clinical utilities for most uses, tumor-associated antigens can be used for monitoring patients with metastatic disease. In addition, markers of tumor biology such as the circulating extracellular domain of HER2/neu might be useful in determining not only prognosis, but also response to specific treatments. However, further

investigations are required to further assess the utility of individual tumor markers for specific clinical uses.

L5 ANSWER 22 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1998:319540 BIOSIS

DOCUMENT NUMBER: PREV199800319540

TITLE: Effects of specific antibodies against the
extracellular domain of the **HER2/neu** on
tyrosine phosphorylation and cell proliferation of SKBR3
breast cancer cell line.

AUTHOR(S): Shao, Hongxia; Qin, Huilian; Li, Xiaohua; et al.

CORPORATE SOURCE: Dep. Immunol., Shanghai Med. Univ., Shanghai 200032 China

SOURCE: Zhonghua Weishengwuxue He Mianyixue Zazhi, (May, 1998)
Vol.

18, No. 3, pp. 220-223.

ISSN: 0254-5101.

DOCUMENT TYPE: Article

LANGUAGE: Chinese

SUMMARY LANGUAGE: Chinese; English

AB Effect of specific McAbs against the **extracellular** domain of the
HER2/neu on tyrosine phosphorylation and cell proliferation of
SKBR3 breast cancer cell line were analyzed with Western blot technique
and antibody dependent specific cell proliferation assay. The results
showed that McAb c-neu-5 enhanced tyrosine phosphorylation of p185 and

had
no distinct function on SKBR3 cell proliferation, yet McAb c-neu-2
inhibited both tyrosine phosphorylation and cell proliferation. Based on
these experiments, we further collected 14 sera of breast cancer
patients, separated and purified the sera IgG. 5 Anti-HER2/neu positive
sera IgG were further selected from patients with breast cancer with

ELISA
method. Cell proliferation assay showed that 3 of 5 sera IgG could
inhibit
cell proliferation of SKBR3. Then we selected 1 positive sera IgG which
could inhibit cell proliferation to test cell tyrosine phosphorylation of
SKBR3. The result showed that this patient sera IgG could also inhibit
tyrosine phosphorylation. Therefore, It suggests that the possible
mechanism of the inhibition of tumor growth by anti-HER2/neu specific
antibody probably through interfering with the activation of signal
transduction system.

L5 ANSWER 23 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1998:152857 BIOSIS

DOCUMENT NUMBER: PREV199800152857

TITLE: Monoclonal antibodies targeted to breast cancer cells.

AUTHOR(S): Park, J. M.; Yang, X.; Press, M. F.

CORPORATE SOURCE: Dep. Pathol., Univ. Southern Calif. Sch. Med., Los
Angeles,

CA USA

SOURCE: Journal of Investigative Medicine, (Jan., 1998) Vol. 46,
No. 1, pp. 102A.

Meeting Info.: Meeting of the Western Section of the
American Federation for Medical Research Carmel,
California, USA February 5-7, 1998 American Federation for
Medical Research
. ISSN: 1081-5589.

DOCUMENT TYPE: Conference

LANGUAGE: English

L5 ANSWER 24 OF 59 MEDLINE

DUPLICATE 12

ACCESSION NUMBER: 97358724 MEDLINE

DOCUMENT NUMBER: 97358724

TITLE: Prediction of response to antiestrogen therapy in advanced
breast cancer patients by pretreatment circulating levels
of **extracellular** domain of the **HER-**

2 neu protein.
AUTHOR: Tamauchi H; O'Neill A; Gelman R; Jarney W; Tenney D Y;
Hosch S; Hayes D F
CORPORATE SOURCE: Lombardi Cancer Center, Department of Medicine, Georgetown
University Medical Center, Washington, DC, USA.
CONTRACT NUMBER: CA64057 (NCI)
SOURCE: JOURNAL OF CLINICAL ONCOLOGY, (1997 Jul) 15 (7) 2518-25.
Journal code: JCO. ISSN: 0732-183X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199710

AB PURPOSE: Overexpression of the HER-2/c-neu/c-erbB2 proto-oncogene is associated with a worse prognosis in patients with breast cancer, perhaps due to an association of the HER-2 proto-oncogene protein with resistance to hormone and/or chemotherapy. Circulating levels of the

extracellular domain (ECD) of the HER-2/c-neu-related protein (NRP) are elevated in 20% to 40% of patients with metastatic breast cancer. We investigated whether pretreatment levels of NRP predict response to hormone therapy (HT). MATERIALS AND METHODS: Circulating NRP levels were determined in 94 patients who participated in a randomized trial of three different doses of the antiestrogen, droloxifene (DRO), as first-line HT for metastatic breast cancer.

RESULTS: NRP levels were elevated ($>$ or $=$ 5,000 U/mL) in 32 of 94 patients (34%). Only three of 32 patients (9%) with elevated NRP levels responded to DRO, compared with 35 of 62 (56%) with nonelevated NRP levels ($P = .00001$).

Low pretreatment NRP level was the most powerful predictor of response to DRO (odds ratio of response, 22.4; $P = .0001$). Elevated pretreatment NRP levels were also associated with a shorter time to progression (TTP) and survival duration. CONCLUSION: Pretreatment circulating NRP levels

predict a low likelihood of benefit from HT, specifically DRO, in patients with estrogen receptor (ER)-positive and/or progesterone receptor (PgR)-positive or receptor-unknown metastatic breast cancer, even when adjusted for other known predictive factors, such as ER and/or PgR

levels, site of disease, disease-free interval from primary treatment to recurrence, and prior adjuvant chemotherapy. These data suggest that pretreatment NRP levels may be useful in deciding whether to treat a patient who otherwise appears to be likely to respond to HT.

L5 ANSWER 25 OF 59 MEDLINE DUPLICATE 13
ACCESSION NUMBER: 1998060590 MEDLINE
DOCUMENT NUMBER: 98060590
TITLE: Soluble HER-2/neu neutralizes biologic effects of anti-HER-2/neu antibody on breast cancer cells in vitro.
AUTHOR: Brodowicz T; Wiltchke C; Budinsky A C; Krainer M; Steger G
G; Zielinski C C
CORPORATE SOURCE: Clinical Division of Oncology, University Hospital, Vienna,
Austria.
SOURCE: INTERNATIONAL JOURNAL OF CANCER, (1997 Dec 10) 73 (6) 875-9.
Journal code: GQU. ISSN: 0020-7136.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199803

AB Amplification and over-expression of the HER-2/neu proto-oncogene are associated with poor prognosis in women with both node-positive and

node-negative breast cancer. Therefore, the encoded surface glycoprotein represents an attractive target for cancer immunotherapies. Furthermore, the **extracellular** domain of **HER-2/neu** is released from the cell surface by proteolytic cleavage. In the present experiments, we investigated the potential biologic effects of soluble HER-2/neu with particular emphasis on its interaction with anti-HER-2/neu antibodies. A monoclonal antibody specific for the **extracellular** domain of **HER-2/neu** dose dependently inhibited the proliferation of highly HER-2/neu-expressing SK-BR-3 and BT-474 breast cancer cells but had no effect on the proliferation of weakly to moderately HER-2/neu-expressing MCF-7, HBL-100 and ZR-75-1 breast cells. Addition of SK-BR-3 or BT-474 cell supernatants with high concentrations of soluble HER-2/neu led to a neutralization of anti-HER-2/neu antibody-mediated inhibition of proliferation due to a binding of soluble HER-2/neu by the antibody, which could be demonstrated by immunoprecipitation. Furthermore, the ability of anti-HER-2/neu antibodies to mediate antibody-dependent cellular cytotoxicity (ADCC) by lymphokine-activated killer cells was assessed. Cytolysis of SK-BR-3 tumor cells was increased significantly in the presence of anti-HER-2/neu antibodies. Similar to the proliferation inhibition, ADCC was neutralized by addition of soluble HER-2/neu-containing supernatants. Our data suggest that tumors rich in HER-2/neu might thus escape certain steps of immunologic control by neutralizing biologic activities of anti HER-2/neu antibodies due to the presence of soluble HER-2/neu.

L5 ANSWER 26 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1997:221412 BIOSIS

DOCUMENT NUMBER: PREV199799513128

TITLE: Remodeling domain interfaces to enhance heterodimer formation.

AUTHOR(S): Zhu, Zhenping; Presta, Leonard G.; Zapata, Gerardo; Carter,

Paul (1)

CORPORATE SOURCE: (1) Dep. Mol. Oncol., Genetech Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080 USA

SOURCE: Protein Science, (1997) Vol. 6, No. 4, pp. 781-788. ISSN: 0961-8368.

DOCUMENT TYPE: Article

LANGUAGE: English

AB An anti-p185-HER2/anti-CD3 humanized bispecific diabody was previously constructed from two cross-over single-chain Fv in which V-H and V-L domains of the parent antibodies are present on different polypeptides. Here this diabody is used to evaluate domain interface engineering strategies for enhancing the formation of functional heterodimers over inactive homodimers. A disulfide-stabilized diabody was obtained by introducing two cysteine mutations, V-L L46C and V-H D101C, at the anti-p185-HER2 V-L/V-H interface. The fraction of recovered diabody that was functional following expression in *Escherichia coli* was improved for the disulfide-stabilized compared to the parent diabody (gt 96% versus 72%), whereas the overall yield was gt 60-fold lower. Eleven "knob-into-hole" diabodies were designed by molecular modeling of sterically complementary mutations at the two V-L/V-H interfaces. Replacements at either interface are sufficient to improve the fraction

of

functional heterodimer, while maintaining overall recoverable yields and affinity for both antigens close to that of the parent diabody. For example, diabody variant v5 containing the mutations V-L Y87A:F98M and

V-H

V37F:L45W at the anti-p185-HER2 V-L/V-H V-L/V-H interface was recovered

as

92% functional heterodimer while maintaining overall recovered yield within twofold of the parent diabody. The binding affinity of v5 for

p185-

HER2 extracellular domain and T cells is eightfold weaker and twofold stronger than for the parent diabody, respectively. Domain interface remodeling based upon either sterically complementary mutations or interchain disulfide bonds can facilitate the production of

a

functional diabody heterodimer. This study expands the scope of domain interface engineering by demonstrating the enhanced assembly of proteins interacting via two domain interfaces.

L5 ANSWER 27 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1997:232100 BIOSIS

DOCUMENT NUMBER: PREV199799531303

TITLE: In-frame deletions in the **HER2**
extracellular domain confer an altered phenotype in
transfected 3T3 cells.

AUTHOR(S): Lewis Phillips, G. D.; Williams, P. W.; McMurtrey, A. E.;
Fendly, B. M.

CORPORATE SOURCE: ~~Genentech Inc., San Francisco, CA 94080 USA~~

SOURCE: Proceedings of the American Association for Cancer
Research

Annual Meeting, (1997) Vol. 38, No. 0, pp. 283.

Meeting Info.: Eighty-eighth Annual Meeting of the

American

Association for Cancer Research San Diego, California, USA
April 12-16, 1997

ISSN: 0197-016X.

DOCUMENT TYPE: Conference; Abstract

LANGUAGE: English

L5 ANSWER 28 OF 59 MEDLINE

DUPLICATE 14

ACCESSION NUMBER: 1998035672 MEDLINE

DOCUMENT NUMBER: 98035672

TITLE: Fractionation and characterization of polyclonal
antibodies

using three progressively more chaotropic solvents.

AUTHOR: Narhi L O; Caughey D J; Horan T P; Kita Y; Chang D;
Arakawa

T

CORPORATE SOURCE: Amgen Inc., Amgen Center, Thousand Oaks, California,
91320-1789, USA.

SOURCE: ANALYTICAL BIOCHEMISTRY, (1997 Nov 15) 253 (2) 246-52.

Journal code: 4NK. ISSN: 0003-2697.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199802

AB In the previous paper we described the effect of several different solvents on the structure of antibodies and demonstrated that 0.1 M glycine, pH 2.9, 7 M urea, pH 4.0, and 6 M guanidine-HCl, pH 4.0, unfold the antibodies to different degrees. Antibodies can be refolded from all of these solvents by dialysis. Polyclonal antibodies (pAbs) are a mixture of antibodies which recognize and bind different epitopes on the same antigen, with the strength of the antigen-antibody binding varying with each subpopulation. When rabbit antisera to the **extracellular** domain of **Her2** receptor (sHer2), derived from Chinese hamster ovary cells, was applied to an antigen column, bound pAbs were recovered with a step-wise elution of 0.1 M glycine, pH 2.9 (44% of the total recovered pAb), 7 M urea, pH 4.0 (29%), and 6 M guanidine-HCl, pH 4.0 (27%), with baseline resolution between them. Fluorescence spectra of the pAbs confirmed that the 0.1 M glycine pH 2.9 sample had near-native structure, the pAbs in 7 M urea, pH 4.0, were partially unfolded, and the pAbs in the 6 M guanidine-HCl, pH 4.0, were totally unfolded. The

glycine-

or urea-eluted sample was refolded by dialysis into PBS, while the

guanidine-HCl-eluted sample was first dialyzed into the 7 M urea pH 4.0 buffer and then into PBS. The refolded material from glycine or urea had native-like spectra, while the spectrum of the protein refolded from 6 M guanidine-HCl was slightly perturbed. All three of these subpopulations of pAbs formed antigen-antibody complexes which could be isolated by gel-filtration chromatography, precipitated sHer2 during immunoprecipitation, and recognized sHer2 in Western blots. The guanidine-HCl-eluted material was most sensitive for Western blotting. Identical results were obtained with pAbs applied either in the batch mode or to the top of the column, indicating that antibody aggregation which may occur when applied from the top of the column is not responsible for the distribution of pAbs into different subpopulations. These results indicate that the sequential use of these three increasingly chaotropic solvents to elute antibodies results in both increased recovery of antibodies and fractionation of pAbs into subpopulations with potentially different antigen-binding characteristics. Copyright 1997 Academic Press.

L5 ANSWER 29 OF 59 MEDLINE

DUPLICATE 15

ACCESSION NUMBER: 1998035671 MEDLINE

DOCUMENT NUMBER: 98035671

TITLE: Effect of three elution buffers on the recovery and structure of monoclonal antibodies.

AUTHOR: Narhi L O; Caughey D J; Horan T; Kita Y; Chang D; Arakawa T

CORPORATE SOURCE: Amgen Inc., Thousand Oaks, California, 91320-1789, USA.

SOURCE: ANALYTICAL BIOCHEMISTRY, (1997 Nov 15) 253 (2) 236-45.

Journal code: 4NK. ISSN: 0003-2697.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199802

AB Antibodies are routinely purified by acid/salt elution from antigen affinity columns. The antibodies recovered with this procedure are active,

but the recovery of protein is often low. We investigated the effect of acid and other denaturing or chaotropic solvents on the conformation of monoclonal antibodies (mAbs) made against the **extracellular** region of **Her2** receptor (sHer2) derived from Chinese hamster ovary cells. The mAb remain almost completely folded in the 0.1 M

glycine,

pH 2.9, commonly used for elution, with the beta-sheet secondary

structure

intact, and only very small changes detected in the environment of the tryptophans. In 7 M urea, 50 mM NaAc pH 4.0, the antibody was partially unfolded, with the Trp environment further perturbed and some of the beta-sheet structure converted to disordered structure. In 6 M guanidine HCl, 50 mM NaAc, pH 4.0, the antibody is completely unfolded, with no secondary or tertiary structure present. The antibodies exposed to

glycine

or urea were refolded by dialysis into phosphate-buffered saline (PBS), while the guanidine HCl-denatured antibodies were refolded by dialysis into 7 M urea, pH 4.0, followed by dialysis into PBS. The refolded antibodies were capable of forming antigen-antibody complexes which could be isolated by gel filtration chromatography. Two different mAbs were subjected to immunoaffinity chromatography on sHer2-Sepharose. mAb86 was eluted by 0.1 M Gly, pH 2.9, while mAb52 was eluted with the 7 M urea, 50 mM NaAc, pH 4.0. The isolated antibodies were refolded by dialysis into PBS, analyzed for their ability to recognize native sHer2 by immunoprecipitation, and denatured sHer2 by Western blot analysis. Both preparations recognized the native protein, but precipitated slightly different forms of sHer2, indicating that they might recognize different epitopes. The mAb52 is a more sensitive reagent for Western blot

analysis.

Thus, this procedure can be used to recover antibodies which would not be recovered with glycine as the only eluate. It is also possible that the antibodies can be fractionated by the different eluants into populations which can be used for different applications. Copyright 1997 Academic Press.

L5 ANSWER 30 OF 59 MEDLINE

DUPLICATE 16

ACCESSION NUMBER: 1998119293

MEDLINE

DOCUMENT NUMBER: 98119293

TITLE: Anti-HER2 immunoliposomes for targeted therapy of human tumors.

AUTHOR: Park J W; Hong K; Kirpotin D B; Meyer O; Papahadjopoulos D;

Benz C C

CORPORATE SOURCE: Department of Medicine, University of California, San Francisco 94143, USA.. johnpark@quickmail.ucsf.edu

CONTRACT NUMBER: P50-CA 58207-01 (NCI)

SOURCE: ~~CANCER LETTERS, (1997 Oct 14) 118 (2) 153-60~~

Journal code: CMX. ISSN: 0304-3835.

PUB. COUNTRY: Ireland

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199804

AB Anti-HER2 immunoliposomes (ILs) have been constructed by conjugation of Fab' fragments of recombinant humanized monoclonal antibody rhuMabHER2 to small sterically stabilized unilamellar liposomes, to create a targeted drug delivery vehicle for the treatment of HER2 (c-erbB-2, neu)-overexpressing cancers. Parameters affecting in vitro binding and internalization of ILs include liposome composition, Fab' linkage site

and

Fab' density. Anti-HER2 ILs have been constructed to optimize intracellular drug delivery. Doxorubicin (dox)-loaded ILs are highly stable and exhibit prolonged circulation in rats. In nude mice bearing HER2-overexpressing tumor xenografts, anti-HER2 ILs administered i.v. resulted in efficient tumor localization, with penetration of the ILs throughout the tumor mass and accumulation within tumor cells. In contrast, non-targeted liposomes resulted in **extracellular** tumor accumulation only. In multiple **HER2**-overexpressing human breast tumor xenograft models, treatment with dox-loaded anti-HER2 ILs produces significantly increased antitumor cytotoxicity as compared to free dox or dox-loaded non-targeted liposomes and significantly less systemic

toxicity

than free dox. To explore further the intracellular delivery advantages of

ILs, anti-HER2 ILs bearing cationic lipids are being developed for nucleic

acid delivery. These cationic immunoliposomes mediate efficient and specific transfection of target cells with reporter genes, as well as intracellular delivery of labeled oligonucleotides. Thus, anti-HER2 ILs represent an efficient and feasible strategy to achieve targeted intracellular delivery of therapeutic agents.

L5 ANSWER 31 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1998:69783 BIOSIS

DOCUMENT NUMBER: PREV199800069783

TITLE: Increased levels of circulating HER2 ECD in response to anti-HER2 antibody therapy.

AUTHOR(S): Park, J. W. (1); Colbern, G.; Nuijens, A.; Baselga, J.; McMillan, A.; Henderson, I. C.; Papahadjopoulos, D.; Benz, C. C.

CORPORATE SOURCE: (1) UCSF, San Francisco, CA 94143 USA

SOURCE: Breast Cancer Research and Treatment, (Oct., 1997) Vol. 46,

No. 1, pp. 67.

DOCUMENT TYPE: Conference
LANGUAGE: English

L5 ANSWER 32 OF 59 MEDLINE

DUPLICATE 17

ACCESSION NUMBER: 97146463 MEDLINE

DOCUMENT NUMBER: 97146463

TITLE: Sterically stabilized anti-HER2 immunoliposomes: design
and

targeting to human breast cancer cells in vitro.

AUTHOR: Kirpotin D; Park J W; Hong K; Zalipsky S; Li W L; Carter
P;

CORPORATE SOURCE: Benz C C; Papahadjopoulos D
Department of Cellular and Molecular Pharmacology,
University of California, San Francisco 94143, USA..
~~skirpotin@itsa.ucsf.edu~~

CONTRACT NUMBER: P50CA58207 (NCI)

SOURCE: BIOCHEMISTRY, (1997 Jan 7) 36 (1) 66-75.

Journal code: A0G. ISSN: 0006-2960.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199704

AB Liposomes (70-100 nm) of 1-palmitoyl-2-oleoylphosphatidylcholine,
cholesterol, and poly(ethylene glycol) (PEG)-modified
phosphatidylethanolamine (PEG-DSPE) were conjugated to Fab' fragments of

a humanized recombinant MAb against the **extracellular** domain of
HER2/neu to create sterically stabilized immunoliposomes
(anti-HER2 SL) as a drug carrier targeting HER2-overexpressing cancers.
Conjugation employed maleimide-terminated membrane-anchored spacers of

two kinds: a short spacer, providing attachment of Fab' close to the liposome
bilayer, or a long spacer, with Fab' attachment at the distal terminus of
the PEG chain. Confocal microscopy and spectrofluorometry of
HER2-overexpressing breast cancer cells incubated with fluorescently
labeled anti-HER2 SL prepared with either spacer showed binding of
liposomes (8000-23000 vesicles/cell) followed by endocytosis (rate
constant $k_e = 0.012-0.033 \text{ min}^{-1}$) via the coated-pit pathway, evidenced by
intracellular acidification and colocalization with transferrin. Uptake

of anti-HER2 immunoliposomes by breast cancer cells with low HER2
expression,

or after preincubation of cells with free anti-HER2 Fab', was less than
0.2% and 4.3%, respectively, of the uptake by HER2-overexpressing cells.
Increasing PEG-DSPE content (up to 5.7 mol %) in anti-HER2-SL prepared
with the short spacer decreased liposome-cell binding affinity
60-100-fold, while k_e decreased only 2-fold; however, when Fab' fragments
were conjugated via a PEG spacer, both binding affinity and k_e were
unaffected by PEG-DSPE content. Cell binding and internalization of
anti-HER2 immunoliposomes increased at higher surface density of
conjugated Fab' fragments, reaching plateaus at approximately 40
Fab'/liposome for binding and approximately 10-15 Fab'/liposome for
internalization. Uptake of anti-HER2 immunoliposomes correlated with the
cell surface density of HER2 and significantly ($p < 0.005$) correlated

with the antiproliferative effect of the targeting antibody but not with the
total level of cellular HER2 expression. The results obtained were used

to optimize in vivo preclinical studies of anti-HER2 SL loaded with
antineoplastic drugs.

L5 ANSWER 33 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1996:563020 BIOSIS

DOCUMENT NUMBER: PREV199799292376

TITLE: Laminin activates the p185-HER2 oncoprotein and mediates growth inhibition of breast carcinoma cells.

AUTHOR(S): Tagliabue, E. (1); Ardini, E.; Pellegrini, R.; Campiglio, M.; Bufalino, R.; Jeschke, M.; Groner, B.; Colnaghi, M.

I.;

Menard, S.

CORPORATE SOURCE: (1) Div. Experimental Oncol. E, Istituto Nazionale Tumori, Via G. Venezian 1, 20133 Milan Italy

SOURCE: British Journal of Cancer, (1996) Vol. 74, No. 9, pp. 1427-1433.

ISSN: 0007-0920.

DOCUMENT TYPE: Article

LANGUAGE: English

AB The interaction between laminin and the oncoprotein encoded by the ~~c-erbB-2 oncogene was studied in vitro and in vivo in human breast~~ carcinomas. In vitro analysis of breast carcinoma cell lines overexpressing p185-HER2 revealed that laminin, but not fibronectin, induced tyrosine phosphorylation and down-modulation of oncoprotein membrane expression. Laminin also specifically inhibited growth of p185-HER2-positive cell lines. No direct binding between the recombinant **extracellular** domain of p185-HER2 and laminin was found. Induction of oncoprotein down-modulation by anti-integrin antibodies and coprecipitation of the oncoprotein with the beta-4 integrin subunit indicate that the interaction between p185-HER2 and laminin occurs through integrin molecules. The relevance of this in vitro observation was verified in vivo by analysing the prognostic value of p185-HER2 overexpression as a function of laminin production on archival paraffin-embedded sections of 887 primary breast tumours. The results revealed an association between p185-HER2 overexpression and unfavourable prognosis in tumours negative for laminin production, whereas in laminin-producing tumours, the oncoprotein overexpression was not associated with tumour aggressiveness.

L5 ANSWER 34 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1997:103237 BIOSIS

DOCUMENT NUMBER: PREV199799402440

TITLE: Human **HER-2/neu extracellular** domain specific antibodies are detected in some breast cancer patients and can have functional effects.

AUTHOR(S): Disis, M. L.; Shiota, F. M.; Qin, H. L.; Rubin, W. R.; Cheever, M. A.

CORPORATE SOURCE: Univ. Washington, Div. Oncol., Seattle, WA 98195 USA

SOURCE: Breast Cancer Research and Treatment, (1996) Vol. 41, No. 3, pp. 245.

Meeting Info.: 19th Annual San Antonio Breast Cancer Symposium on Breast Cancer Research and Treatment San Antonio, Texas, USA December 11-14, 1996

ISSN: 0167-6806.

DOCUMENT TYPE: Conference; Abstract

LANGUAGE: English

L5 ANSWER 35 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1996:123937 BIOSIS

DOCUMENT NUMBER: PREV199698696072

TITLE: High level secretion of a humanized bispecific diabody from

Escherichia coli.

AUTHOR(S): Zhu, Zhenping; Zapata, Gerardo; Shalaby, Refaat; Snedecor, Brad; Chen, Han; Carter, Paul (1)

CORPORATE SOURCE: (1) Dep. Mol. Oncol., Genentech Inc., 460 Point San Bruno Boulevard, South San Francisco, CA 94080 USA

SOURCE: Bio-Technology (New York), (1996) Vol. 14, No. 2, pp. 192-196.

ISSN: 0733-222X.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Clinical development of bispecific antibodies (BsAb) has been effectively stymied by the lack of efficient production methods. We therefore attempted to produce a humanized BsAb fragment using an expression system that has proved very successful for secretion of monospecific Ab fragments

from E. coli. An anti-p185-HER2/anti-CD3 BsF(ab')-2 was first recast into the diabody format and then periplasmically secreted from E. coli grown to

high cell density in a fermentor. The diabody was recovered in very high yield (up to 935 mg/l) after protein A purification and predominantly (gtoreq 80%) as a dimer as judged by size exclusion chromatography.

Diabody

~~dimers were found to be mainly functional heterodimers (apprx 75%) by~~

titration with p185-**HER2 extracellular** domain. The

diabody binds p185-**HER2 extracellular** domain and human

T lymphocytes with affinities close to those of the parent BsF(ab')-2.

Furthermore, the diabody is capable of simultaneous binding to tumor

cells

overexpressing p185-HER2 and CD3 on T cells as shown by cellular resetting. The diabody is equally potent as the parent BsF(ab')-2 in retargeting IL-2 activated T-enriched peripheral blood lymphocytes to

lyse

tumor cells overexpressing p185-HER2.

L5 ANSWER 36 OF 59 MEDLINE

DUPLICATE 18

ACCESSION NUMBER: 96222282 MEDLINE

DOCUMENT NUMBER: 96222282

TITLE: Humoral and cellular responses raised against the human HER2 oncoprotein are cross-reactive with the homologous product of the new proto-oncogene, but do not protect rats against B104 tumors expressing mutated neu.

AUTHOR: Taylor P; Gerder M; Moros Z; Feldmann M

CORPORATE SOURCE: Center for Experimental Medicine, Venezuelan Institute for Scientific Research, IVIC, Caracas, Venezuela..
ptaylor@medicina.ivic.ve

SOURCE: CANCER IMMUNOLOGY, IMMUNOTHERAPY, (1996 Mar) 42 (3) 179-84.

JOURNAL code: CN3. ISSN: 0340-7004.

PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199609

AB The neu proto-oncogene encodes a plasma membrane protein belonging to the epidermal growth factor receptor family. The cell line B104, derived from BDIX rat neuroblastoma, carries a point mutation in neu, and forms a tumor

when injected into these rats. The human homologue of the neu oncogene (here called HER2) is overexpressed in certain types of cancer. Rats were immunized with HER2 protein (HER2) to investigate a possible cross-reaction between the homologous proteins which could protect them against subsequent inoculation with B104. Specific antibody in the serum was measured by cell-based enzyme-linked immunoabsorbent assay and fluorescence immunocytochemistry, and delayed-type hypersensitivity by an ear assay. Sera from animals immunized with the **HER2 extracellular** domain (**HER2-ECD**) reacted with both HER2- and neu-expressing cells. In the ear assay, a significant cellular response to both HER-ECD (P < 0.05) and neu protein (P < 0.001) was observed in HER2-ECD-immunized rats. However, the growth of B104 tumors

in

rats was not affected by preimmunization with HER2-ECD. The results indicate that an autoreactive immune response to neu was induced by immunization with HER2-ECD, but was too weak to affect the growth of the neu-bearing tumor.

L5 ANSWER 37 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1997:33318 BIOSIS

DOCUMENT NUMBER: PREV199799339721

TITLE: 186-Re-labeled antibodies to p185-HER2 as HER2-targeted radioimmunopharmaceutical agents: Comparison of physical and biological characteristics with 125I and 131I-labeled counterparts.

AUTHOR(S): Kotts, C. E. (1); Su, F. M.; Leddy, C.; Dodd, T.; Scates, S.; Shalaby, M. R.; Wirth, C. M.; Giltinan, D.; Schroff, R.

W.; Fritzberg, A. R.; Shepard, H. M.; Slamon, D. J.; Hutchins, B. M.

~~CORPORATE SOURCE: (1) Genentech Inc., Mail Zone 65, 460 Point San Bruno Blvd., S. San Francisco, CA 94080 USA~~

SOURCE: Cancer Biotherapy & Radiopharmaceuticals, (1996) Vol. 11, No. 2, pp. 133-144.
ISSN: 1084-9785.

DOCUMENT TYPE: Article

LANGUAGE: English

AB Overexpression of the HER2/neu protooncogene has been shown to correlate with poor clinical prognosis. A murine monoclonal antibody (4D5) directed against the **extracellular** domain (ECD) of p185-**HER2** has been shown to inhibit in vitro and in vivo growth of carcinomas overexpressing HER2 and has been humanized (rhuMab HER2). The objective

of

the study was the identification of an agent which might be useful for in vitro studies, tumor imaging and/or radioimmunotherapy by linking beta-emitting radionuclides to these HER2-targeted antibodies. Murine 4D5 and humanized rhuMab HER2 were radiolabeled with 125I, 131I or 186Re. Physical characteristics (TCA precipitability, SDS-PAGE, size exclusion chromatography), binding affinities to the HER2 ECD (in an ELISA and on SK-BR-3 cells) and antiproliferative activities of the radiolabeled antibodies were determined. Although 131I-4D5 and 131I-rhuMab HER2

usually

retained gt 85% ECD binding, they exhibited increased aggregation and fragment content, drastically reduced antiproliferative activities and poor stability upon storage at 4 degree C. For these antibody preparations, conservation of binding did not necessarily correlate with preservation of bioactivity indicating the importance of bioactivity determinations in radiolabeled antibody studies. Conversely, 4D5 and rhuMab HER2 labeled with 125I or 186Re maintained physical properties,

ECD

binding, antiproliferative activities and were stable upon storage at 4 degree C for at least 8 days. The superior retention of physical and biological characteristics of 186Re-labeled 4D5 and rhuMab HER2 compared with their 131I-labeled counterparts suggests the potential for their use as radioimaging and radioimmunotherapeutic agents in the treatment of

HER2

overexpressing tumors.

L5 ANSWER 38 OF 59 MEDLINE

ACCESSION NUMBER: 96275217 MEDLINE

DOCUMENT NUMBER: 96275217

TITLE: Serum (circulating) tumor markers for breast cancer.

AUTHOR: Hayes D F

CORPORATE SOURCE: Breast Evaluation Center, Dana-Farber Cancer Institute, Harvard Medical School, Boston, MA 02115, USA.

SOURCE: RECENT RESULTS IN CANCER RESEARCH, (1996) 140 101-13.

Ref:

Journal code: R1Y. ISSN: 0080-0071
PUB. COUNTRY: GERMANY: Germany, Federal Republic of
Journal; Article; (JOURNAL ARTICLE)
General Review; (REVIEW)
(REVIEW, TUTORIAL)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199611

AB Many circulating markers have been proposed for breast cancer, with potential utility for identification, screening, prognosis, detection, or monitoring. Of the available markers, those with the greatest promise include circulating tumor markers that provide an indication of clinical course, such as CA15-3 and CEA, and novel markers such as BrCa1, antibodies to p53, antibodies to HER-2/neu, indicators of angiogenesis, and the **extracellular** domain of HER-2/neu. However, the precise clinical utilities of all of these markers have yet to be determined. It is especially important that the relative independence of the markers in relation to other available markers be determined so as to avoid the unnecessary cost and expense of redundancy. Moreover, it is important that the clinician be aware of the limitations in both sensitivity and specificity of each marker so as not to over- or under-interpret the predictive value of any test.

L5 ANSWER 39 OF 59 MEDLINE DUPLICATE 19
ACCESSION NUMBER: 96400216 MEDLINE
DOCUMENT NUMBER: 96400216
TITLE: ErbB receptor activation, cell morphology changes, and apoptosis induced by anti-Her2 monoclonal antibodies.
AUTHOR: Kita Y; Tseng J; Horan T; Wen J; Philo J; Chang D; Ratzkin B; Pacifici R; Brankow D; Hu S; Luo Y; Wen D; Arakawa T; Nicolson M
CORPORATE SOURCE: Department of Immunology, Amgen Inc., Amgen Center, Thousand Oaks, California 91320, USA.
SOURCE: BIOCHEMICAL AND BIOPHYSICAL RESEARCH COMMUNICATIONS, (1996 Sep 4) 226 (1) 59-69.
Journal code: 9Y8. ISSN: 0006-291X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199612

AB A panel of mAbs were generated against the purified soluble form of erbB2/

Her2 receptor, corresponding to the **extracellular** region of the receptor, and examined for their ability to mimic the receptor ligand. Some of the mAbs strongly induced tyrosine phosphorylation of 180-185 kDa proteins, including not only Her2 but also Her3 and Her4 receptors, when they were expressed on the surface of breast cancer cells.

These mAbs do not cross-react with Her3 or Her4 as demonstrated by competition study. Receptor phosphorylation was also observed with the cell lines transfected with Her2 or a chimeric receptor consisting of the **extracellular** domain of Her2 and the transmembrane and cytoplasmic domains of epidermal growth factor receptor. Selected mAbs were tested for their ability to change cell morphology, and one specific mAb, mAb74, induced cell morphology changes and apoptosis.

L5 ANSWER 40 OF 59 MEDLINE DUPLICATE 20
ACCESSION NUMBER: 96025862 MEDLINE
DOCUMENT NUMBER: 96025862
TITLE: Binding of Neu differentiation factor with the **extracellular** domain of Her2 and Her3.
AUTHOR: Horan T; Wen J; Arakawa T; Liu N; Brankow D; Hu S; Ratzkin B; Philo J S
CORPORATE SOURCE: Amgen Inc., Amgen Center, Thousand Oaks, California 91320,

SOURCE: JOURNAL OF BIOLOGICAL CHEMISTRY, 1995 Oct 13) 270 (41)
24604-8.
Journal code: HIV. ISSN: 0021-9258.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals; Cancer Journals
ENTRY MONTH: 199602

AB The interaction of neu differentiation factor (NDF) with the **extracellular** domains of **Her2** (sHer2) and Her3 (sHer3) have been studied using native gels, light scattering, and sedimentation equilibrium. The full-length NDF beta 2 was shown to bind sHer3 with a dissociation constant of 26 +/- 9 nM, while it showed a 1000-fold weaker binding to sHer2. Taken together, these results demonstrate that NDF is a high affinity ligand for Her3, but not for Her2. No increase in affinity of the NDF beta 2 for sHer3 was observed upon addition of sHer2 to the

NDF beta 2-sHer3 mixture. Binding of NDF beta 2 to sHer3 did not induce receptor dimerization or oligomerization, the stoichiometry being one sHer3 per one NDF molecule. This finding suggests that transmembrane and/or intracellular domains of receptor family members or perhaps additional unidentified components may be involved in NDF induced dimerization and autophosphorylation, or alternatively, that dimerization is not the mechanism for Her3 autophosphorylation and signal transduction.

L5 ANSWER 41 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1995:23320 BIOSIS

DOCUMENT NUMBER: PREV199598037620

TITLE: Antigenic and immunogenic mimicry of the HER2/neu oncoprotein by phage-displayed peptides.

AUTHOR(S): Orlandi, Rosaria (1); Menard, Sylvie; Colnaghi, Maria I.; Boyer, Cinda M.; Felici, Franco

CORPORATE SOURCE: (1) Div. Experimental Oncology E, Ist. Nazionale Studio Cura Tumori, Via Venezian 1, I-20133 Milan Italy

SOURCE: European Journal of Immunology, (1994) Vol. 24, No. 11, pp.

2868-2873.

ISSN: 0014-2980.

DOCUMENT TYPE: Article

LANGUAGE: English

AB To recover peptides that antigenically and immunogenically mimic the p185-HER2 oncoprotein, we selected the phage-peptide libraries pVIII-9aa and pVIII-9aa.Cys using murine monoclonal antibodies (mAb) MGr2 and MGr6, directed against two distinct epitopes of the p185-**HER2 extracellular** domain. Phage-displayed peptides containing consensus amino acid motifs were recovered and shown to compete specifically for mAb binding on tumor cells that overexpress p185-HER2. The deduced amino acid sequence of the peptides suggests that both epitopes defined by the mAb on p185-HER2 are discontinuous and that hydrophobic interactions are involved in binding with the mAb. A phage clone displaying the GPLDSLFAQ peptide elicited a specific immune response

against the p185-HER2 in BALB/c mice, demonstrating that this phage-displayed peptide represents an immunological equivalent of the

MGr2 epitope on p185-HER2 and might be used as a substitute for this oncoprotein in in vitro and in vivo immunological studies.

L5 ANSWER 42 OF 59 MEDLINE

DUPLICATE 21

ACCESSION NUMBER: 94155127 MEDLINE

DOCUMENT NUMBER: 94155127

TITLE: Prevalence and significance of HER-2/neu expression in early epithelial ovarian cancer.

AUTHOR: Bin S C; Finstad C L; Federici G; Scheiner L; Lloyd K
Hoskins W J
CORPORATE SOURCE: Memorial Sloan-Kettering Cancer Center, New York, New
York.
CONTRACT NUMBER: CA 52477 (NCI)
CA 08478 (NCI)
SOURCE: CANCER, (1994 Mar 1) 73 (5) 1456-9.
Journal code: CLZ. ISSN: 0008-543X.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer
Journals
ENTRY MONTH: 199406

AB BACKGROUND. Although expression of the HER-2/neu oncogene may be of some prognostic importance in advanced ovarian cancer, its role in early-stage disease has not been established. The current study examined the prevalence and significance of HER-2/neu expression in early epithelial ovarian cancer. METHODS. The authors analyzed the expression of HER-2/neu on frozen tumor specimens from 40 patients with early epithelial ovarian cancer using the indirect immunoperoxidase technique with monoclonal antibodies that detect epitopes on the **extracellular** domain of the HER-2/neu protein. All patients underwent comprehensive surgical staging. HER-2/neu expression was graded as negative, weak, moderate (1+ to 2+), or strong (3+). Complete clinical data and long-term follow up were available for all patients. RESULTS.

The distribution of patients by stage was as follows: Stage IA, 6; IB, 0; IC, 14; IIA, 4; IIB, 6; IIC, 10. The mean patient age was 53 years. Fourteen patients had serous tumors; nine, endometrioid; eight, clear cell; eight, mucinous; and one, undifferentiated. Intratumoral heterogeneity of HER-2/neu expression was observed with most specimens. In eight specimens (20%), some areas of the tumor showed strong (3+) expression, beyond the level that can be seen in normal ovarian epithelium. Twenty-eight specimens (70%) showed moderate (1+ to 2+) staining, whereas four specimens (10%) showed negative or weak staining. At a mean follow-up

time among surviving patients of 32 months, 15 patients (37%) have had cancer recurrence. No statistically significant relationship was found between HER-2/neu expression and survival, disease-free survival, stage, or grade.

A significant increase was found in 3+ expression of HER-2/neu in clear cell tumors. CONCLUSION. Consistent HER-2/neu overexpression occurs infrequently in early ovarian cancer, making it unlikely that such overexpression is a general early event in ovarian carcinogenesis. HER-2/neu expression does not appear to be a strong prognostic marker in early epithelial ovarian cancer.

L5 ANSWER 43 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1995:65936 BIOSIS
DOCUMENT NUMBER: PREV199598080236
TITLE: Immunotoxins to the HER-2 oncogene product: Functional and ultrastructural analysis of their cytotoxic activity.
AUTHOR(S): Di Lazzaro, Claudia; Digiesi, Giovanna; Tecce, Raffaele; Lotti, Lavinia V.; Torrisi, Maria Rosaria; Natali, Pier G.
(1)
CORPORATE SOURCE: (1) Immunol. Lab., Regina Elena Cancer Inst., Via delle Messi D'oro 156, I-00158 Rome Italy
SOURCE: Cancer Immunology Immunotherapy, (1994) Vol. 39, No. 5, pp. 318-324.
ISSN: 0340-7004.
DOCUMENT TYPE: Article
LANGUAGE: English
AB Two immunotoxins were prepared using monoclonal antibodies (mAb) directed

towards two distinct epitopes of the gp185-HER-~~extracellular~~ domain, and the type 1 ribosome inactivating protein (RIP) plant toxin saporin 6. Cell protein synthesis inhibition assay reveals that the immunotoxins display a potent and specific cytotoxicity that is characterized by a slow rate, since the time required to inhibit incorporation of radiolabeled leucine completely ranges from 36 h to 60 h depending on the target cell line and the immunotoxin. Because this feature may hamper the immunotherapeutic use of these conjugates we analysed this further by studying the early phases of internalization of immunotoxins by immunoelectron microscopy. The results of this study have demonstrated that the distribution pattern of the immunotoxins and of the unconjugated mAb over the cell surface overlaps. Similarly the mAb and immunotoxins are internalized into the cell by two different pathways:

via

clathrin-coated pits or via smaller uncoated pits and vesicles. A higher degree of internalization is achieved when the two immunotoxins are used in combination. Unlike the slow kinetics of cell intoxication the process of immunotoxin endocytosis is characterized by a rapid rate of internalization (above 40% at 5 min in the SK-BR-3 cell line). Although these findings provide no clue to explain the mechanisms of the slow rate of cytotoxicity of the two immunotoxins their rapid internalization indicates that these reagents can be exploited in immunotherapeutic approaches to gp185-HER-2-expressing malignancies.

L5 ANSWER 44 OF 59 MEDLINE

DUPLICATE 22

ACCESSION NUMBER: 93204970 MEDLINE

DOCUMENT NUMBER: 93204970

TITLE: A truncated intracellular HER2/neu receptor produced by alternative RNA processing affects growth of human carcinoma cells.

AUTHOR: Scott G K; Robles R; Park J W; Montgomery P A; Daniel J; Holmes W E; Lee J; Keller G A; Li W L; Fendly B M; et al

CORPORATE SOURCE: Cancer Research Institute, University of California, San Francisco 94143-0128.

CONTRACT NUMBER: CA-44768 (NCI)
CA-36773 (NCI)

SOURCE: MOLECULAR AND CELLULAR BIOLOGY, (1993 Apr) 13 (4) 2247-57.
Journal code: NGY. ISSN: 0270-7306.

PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals

ENTRY MONTH: 199306

AB Cloned sequences encoding a truncated form of the HER2 receptor were obtained from cDNA libraries derived from two HER2-overexpressing human breast cancer cell lines, BT-474 and SK-BR-3. The 5' 2.1 kb of the encoded

transcript is identical to that of full-length 4.6-kb HER2 transcript and would be expected to produce a secreted form of HER2 receptor containing only the extracellular ligand binding domain (ECD). The 3' end of the truncated transcript diverges 61 nucleotides before the receptor's transmembrane region, reads through a consensus splice donor site containing an in-frame stop codon, and contains a poly(A) addition site, suggesting that the truncated transcript arises by alternative RNA processing. S1 nuclease protection assays show a 40-fold variation in the abundance of the truncated 2.3-kb transcript relative to full-length 4.6-kb transcript in a panel of eight HER2-expressing tumor cell lines of gastric, ovarian, and breast cancer origin. Expression of this truncated transcript in COS-1 cells produces both secreted and intracellular forms of HER2 ECD; however, immunofluorescent labeling of HER2 ECD protein in MKN7 tumor cells that natively overexpress the 2.3-kb transcript suggests that transcriptionally generated HER2 ECD is concentrated within the perinuclear cytoplasm. Metabolic labeling and endoglycosidase studies suggest that this HER2 ECD (100 kDa) undergoes differential trafficking between the endoplasmic reticulum and Golgi compartments compared with

full-length (185 aa) HER2 receptor. Transfection studies indicate that excess production of HER2 ECD in human tumor cells overexpressing full-length HER2 receptor can result in resistance to the growth-inhibiting effects of anti-HER2 monoclonal antibodies such as muMAb4D5. These findings demonstrate alternative processing of the HER2 transcript and implicate a potentially important growth regulatory role for intracellularly sequestered HER2 ECD in HER2-amplified human tumors.

L5 ANSWER 45 OF 59 MEDLINE

ACCESSION NUMBER: 93161295 MEDLINE

DOCUMENT NUMBER: 93161295

TITLE: Cell growth regulation in epithelial ovarian cancer.

AUTHOR: Bast R C Jr; Boyer C M; Jacobs I; Xu F J; Wu S; Wiener J; Kohler M; Berchuck A

CORPORATE SOURCE: Department of Medicine, Duke University Medical Center, Durham, North Carolina 27710..

CONTRACT NUMBER: R01CA39930 (NCI)

SOURCE: ~~CANCER, (1993 Feb 15) 71 (4 Suppl) 1597-601. Ref: 55~~

Journal code: CLZ. ISSN: 0008-543X.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

General Review; (REVIEW)

(REVIEW, TUTORIAL)

LANGUAGE: English

FILE SEGMENT: Abridged Index Medicus Journals; Priority Journals; Cancer Journals

ENTRY MONTH: 199305

AB BACKGROUND. As in the case of other epithelial neoplasms, most ovarian cancers arise from single clones of cells that have undergone multiple genetic alterations. A comparison of normal and malignant ovarian epithelium has identified several differences in growth regulation by peptide growth factors, protooncogenes, and tumor suppressor genes. METHODS. Recent articles and abstracts have been reviewed. RESULTS. The malignant ovarian epithelial phenotype has been associated with (1) autocrine growth stimulation by transforming growth factor-alpha, (2)

loss of autocrine growth inhibition by transforming growth factor-beta, (3) mutation or amplification of ras in 2-12% of cases, (4) amplification of myc in 23% of specimens, (5) expression of fms in 56% of cases with potential autocrine stimulation by macrophage colony stimulating factor, (6) paracrine stimulation by macrophage products including interleukin-1, interleukin-6 and tumor necrosis factor, (7) overexpression of c-erbB-2 (HER-2/neu) in 30% of cases, and (8) mutation with consequent overexpression of p53 in 50% of advanced ovarian cancers. A poor clinical prognosis is associated with expression or overexpression of the

epidermal

growth factor receptor, fms, and HER-2/neu. Antibodies against the extracellular domain of the HER-2

/neu gene product p185 inhibit the growth of tumor cells that overexpress HER-2/neu and are associated with marked decreases in diacylglycerol levels. The intracellular kinase domain is required for growth

inhibition.

Antibodies that inhibit growth stimulate phosphorylation of intracellular substrates. Ricin A chain monoclonal antibody conjugates that react with p185 also inhibit the growth of tumor cells that overexpress p185. The intracellular kinase region is not required for immunotoxin-mediated killing. Coexpression of HER-2/neu and the epidermal growth factor receptor has been observed in 65% of epithelial ovarian cancers and in a limited number of normal tissue from a fraction of donors. CONCLUSIONS: Multiple alterations in growth factors, protooncogenes and growth factors have been detected in different epithelial ovarian cancers. Inappropriate signalling from receptor tyrosine kinases may be particularly important for ovarian oncogenesis. Drugs that affect tyrosine kinase and

phosphatase

activity deserve attention as potential therapeutic agents for ovarian

cancer. The **extracellular** domains of the **HER-2**
/neu gene product p185 and the epidermal growth factor receptor may
provide useful targets for serotherapy.

L5 ANSWER 46 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1993:367913 BIOSIS

DOCUMENT NUMBER: PREV199396053588

TITLE: Antibody-induced activation of p185-HER2 in the human lung
adenocarcinoma cell line Calu-3 requires bivalency.

AUTHOR(S): Srinivas, Uppugunduri; Tagliabue, Elda; Campiglio,
Manuela;

Menard, Sylvie; Colnaghi, Maria Ines

CORPORATE SOURCE: Dep. Clin. Chem., Univ. Hosp., Linkoping Sweden

SOURCE: Cancer Immunology Immunotherapy, (1993) Vol. 36, No. 6,
pp.

397-402.

ISSN: 0340-7004.

DOCUMENT TYPE: Article

LANGUAGE: English

AB In the present study we utilized two previously described monoclonal
antibodies (mAb), and their respective Fab portions, directed against the
extracellular domain of p185-**HER2**, a transmembrane
glycoprotein with intrinsic tyrosine kinase activity coded by the

HER2/neu

oncogene, to study the mechanism of mAb-induced receptor internalization
and phosphorylation. Fluorescence scan analysis and direct binding of
radiolabelled mAb and their Fab fragments showed that entire MGR2 and

MGR3

mAb were reactive with similar binding affinity on two cell lines (Calu-3
and Sk-Br-3) overexpressing the p185-HER2 receptor, and unreactive on
unrelated cells. The corresponding Fab fragments were positive on the
related cells, but bound with diminished intensity and affinity. Entire
MGR2 and MGR3 induced internalization in both Calu-3 and Sk-Br-3 cells,
whereas their Fab portions were not internalized. When the bivalency of
the MGR2 Fab fragment was artificially reconstituted by incubation with
rabbit anti-(mouse IgG), internalization was obtained. Monovalent binding
of the entire labelled antibodies, obtained in the presence of a
saturating amount of unlabelled antibody, decreased both the rate and the
final amount of internalized antibody. Metabolic labelling and
immunoblotting experiments showed that incubation with entire MGR3
amplified the basal phosphorylation of the p185-HER2 receptor in Calu-3
and Sk-Br-3 cells, whereas MGR3 Fab decreased the signal. Taken together,
our data indicate that antibody-mediated activation of p185-HER2 in

Calu-3

and Sk-Br-3 cells occurs through the dimerization of receptor molecules
and that bivalency of the activating antibody is mandatory for induction
of internalization and phosphorylation of the receptor. Our data support
an allosteric model of activation for the p185-HER2 receptor.

L5 ANSWER 47 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1993:480683 BIOSIS

DOCUMENT NUMBER: PREV199396114283

TITLE: Differential responses of human tumor cell lines to
anti-p185-HER2 monoclonal antibodies.

AUTHOR(S): Lewis, Gail D. (1); Figari, Irene; Fendly, Brian; Wong,
Wai

Lee; Carter, Paul; Gorman, Cori; Shepard, H. Michael
CORPORATE SOURCE: (1) Dep. Cell Analysis, Genentech Inc., 460 Point San
Bruno

Blvd., South San Francisco, CA 93080 USA

SOURCE: Cancer Immunology Immunotherapy, (1993) Vol. 37, No. 4,
pp.

255-263.

ISSN: 0340-7004.

DOCUMENT TYPE: Article

LANGUAGE: English

AB The HER2 protooncogene encodes a receptor tyrosine kinase, p185-HER2. The overexpression of p185-HER2 has been associated with a worsened prognosis in certain human cancers. In the present work we have screened a variety of different tumor cell lines for p185-HER2 expression using both enzyme-linked immunosorbent and fluorescence-activated cell sorting

assays

employing murine monoclonal antibodies directed against the extracellular domain of the receptor. Increased levels of p185-HER2 were found in

breast

(5/9), ovarian (1/6), stomach (2/3) and colorectal (5/16) carcinomas, whereas all kidney and submaxillary adenocarcinoma cell lines tested were negative. Some monoclonal antibodies directed against the **extracellular** domain of p185-HER2 inhibited growth in monolayer culture of breast and ovarian tumor cell lines overexpressing p185-HER2, but had no effect on the growth of colon or gastric adenocarcinomas expressing increased levels of this receptor. The most potent growth-inhibitory anti-p185-HER2 monoclonal antibody in monolayer culture, designated mumAb 4D5 (a murine IgG1-kappa antibody), was also tested in soft-agar growth assays for activity against p185-HER2-overexpressing tumor cell lines of each type, with similar results. In order to increase the spectrum of tumor types potentially susceptible to monoclonal antibody-mediated anti-p185-HER2 therapies, to decrease potential immunogenicity issues with the use of murine

monoclonal

antibodies for human therapy, and to provide the potential for antibody-mediated cytotoxic activity, a mouse/human chimeric 4D5 (chmAb 4D5) and a "humanized" 4D5 (rhumaB 4D5 HER2 antibody) were constructed. Both engineered antibodies, in combination with human peripheral blood mononuclear cells, elicited antibody-dependent cytotoxic responses in accordance with the level of p185-HER2 expression. Since this cytotoxic activity is independent of sensitivity to mumAb 4D5, the engineered monoclonal antibodies expand the potential target population for antibody-mediated therapy of human cancers characterized by the overexpression of p185-HER2.

L5 ANSWER 48 OF 59 MEDLINE

DUPLICATE 23

ACCESSION NUMBER: 92366172 MEDLINE

DOCUMENT NUMBER: 92366172

TITLE: Transformation mediated by the human HER-2 gene independent

of the epidermal growth factor receptor.

AUTHOR: Chazin V R; Kaleko M; Miller A D; Slamon D J

CORPORATE SOURCE: Department of Medicine, University of California, Los Angeles.

CONTRACT NUMBER: CA 36827 (NCI)
GM-07185 (NIGMS)

SOURCE: ONCOGENE, (1992 Sep) 7 (9) 1859-66.
Journal code: ONC. ISSN: 0950-9232.

PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199211

AB Amplification of the HER-2 (c-erbB-2) gene and overexpression of the p185HER-2 gene product is found in approximately one-third of primary human breast and ovarian cancers and is associated with a poor clinical outcome of early relapse and death. The HER-2 gene encodes a cell-surface growth factor receptor with intrinsic tyrosine kinase activity. Wild-type human HER-2 has been shown to act as a potent oncogene when

over-expressed

in mouse fibroblasts. Recent data suggest that the mechanism by which HER-2 mediates transformation requires the interaction of the epidermal growth factor (EGF) receptor. To test whether overexpression of normal human HER-2 can transform cells independently of the EGF receptor, we

have

introduced multiple copies of HER-2 into the EGF receptor-negative cell line, NR6, and have performed assays for both transformation and tumorigenicity. Engineered NR6 cells that overexpress the HER-2 gene product display a highly transformed and tumorigenic phenotype as compared with control cells. Additionally, a monoclonal antibody to the **extracellular** domain of the **HER-2** receptor is able to inhibit the proliferation of the overexpressing cells in vitro as well as tumor growth in vivo. This study provides clear evidence that HER-2-mediated transformation can be achieved independently of the EGF receptor.

L5 ANSWER 49 OF 59 MEDLINE

DUPLICATE 24

ACCESSION NUMBER: 92005459 MEDLINE

DOCUMENT NUMBER: 92005459

TITLE: Requirements for the internalization of a murine monoclonal

~~antibody directed against the HER-2/neu gene product c-erbB-2.~~

AUTHOR: Maier L A; Xu F J; Hester S; Boyer C M; McKenzie S; Bruskin

A M; Argon Y; Bast R C Jr

CORPORATE SOURCE: Department of Medicine, Duke Comprehensive Cancer Center, Duke University Medical Center, Durham, North Carolina 27710.

CONTRACT NUMBER: 5-R01-CA 39930 (NCI)

SOURCE: CANCER RESEARCH, (1991 Oct 1) 51 (19) 5361-9. Journal code: CNF. ISSN: 0008-5472.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199201

AB A murine monoclonal antibody, TA1, is directed against an epitope on the **extracellular** domain of the **HER-2/neu** (c-erbB-2) gene product. Requirements for TA1-induced internalization of c-erbB-2 have been studied using the SKBr3 human breast cancer cell line and several rat fibroblast cell lines that express either wild-type or mutant human c-erbB-2. Internalization of TA1 was monitored by assaying protease-resistant uptake of 125I-labeled TA1, by electron microscopy of gold-labeled TA1, and by inhibition of clonogenic growth of cells incubated with TA1 that had been conjugated with blocked ricin. Similar rates of internalization of TA1 were observed in SKBr3 and in rat fibroblasts that expressed human c-erbB-2. The route of endocytosis was the same as that observed with antibodies against other membrane receptors. Anti-c-erbB-2 and anti-transferrin receptor cointernalized through clathrin-coated pits, coated vesicles, endosomes, and multivesicular bodies. Products of mutant c-erbB-2 that lacked a portion of the tyrosine kinase domain or that lacked most of the cytoplasmic domain were endocytosed in the presence of TA1 as promptly as the wild-type c-erbB-2 product. Slightly more rapid internalization of TA1 was observed in rat cells that expressed c-erbB-2 with a single point mutation in the transmembrane domain. Taken together, our data suggest that neither the intracytoplasmic domain nor receptor phosphorylation is required for antibody-mediated endocytosis of c-erbB-2.

L5 ANSWER 50 OF 59 MEDLINE

ACCESSION NUMBER: 92102670 MEDLINE

DOCUMENT NUMBER: 92102670

TITLE: Fab assembly and enrichment in a monovalent phage display system.

AUTHOR: Garrard L J; Yang M; O'Connell M P; Kelley R F; Henner D J

CORPORATE SOURCE: Department of Cell Genetics, Genentech, Inc., South San Francisco, CA 94080.

SOURCE: BIO/TECHNOLOGY, (1991 Dec) 9 (12) 1373-7.

Journal code: AL1. ISSN: 0733-222X.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: B

ENTRY MONTH: 199204

AB We have developed a system that allows the expression of a single copy of an antibody Fab molecule on the surface of the filamentous bacteriophage M13 and demonstrate the utility of this system for enrichment of specific "Fab phage". A "humanized" version of antibody 4D5 (h4D5) directed

against

the **extracellular** domain of the **HER2** (neu) receptor,

was used as prototype to assess the assembly of Fab molecules on the

phage

~~and to determine the power of the enrichment system. The h4D5 Fab phage~~

showed specific binding to the extracellular domain of the receptor and

exhibited an affinity for its antigen virtually identical to the Fab

itself. By virtue of its antigen binding, the h4D5 Fab phage could be

sorted from a million-fold excess of non-cognate Fab phage in only two

rounds of sorting. Further experiments demonstrated that the h4D5 Fab

phage could be preferentially enriched from mixtures of variant Fab

phages

that had lower affinities for the HER2 receptor.

L5 ANSWER 51 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1991:378412 BIOSIS

DOCUMENT NUMBER: BR41:50802

TITLE: ANTIBODIES AGAINST IMMUNOCHEMICALLY DISTINCT EPITOPES ON THE **EXTRACELLULAR** DOMAIN OF **HER-**

2-NEU C-ERBB-2 INHIBIT GROWTH OF BREAST AND OVARIAN CANCER CELL LINES.

AUTHOR(S): XU F J; RODRIGUEZ G C; WHITAKER R; BOENTE M; BERCHUCK A;

MCKENZIE S; HOUSTON L; BOYER C M; BAST R C JR

CORPORATE SOURCE: DUKE UNIV. MED. CENTER, DURHAM, N.C. 27710.

SOURCE: PROCEEDINGS OF THE 82ND ANNUAL MEETING OF THE AMERICAN ASSOCIATION FOR CANCER RESEARCH, HOUSTON, TEXAS, USA, MAY 15-18, 1991. PROC AM ASSOC CANCER RES ANNU MEET, (1991) 32 (0), 260.

CODEN: PAMREA.

DOCUMENT TYPE: Conference

FILE SEGMENT: BR; OLD

LANGUAGE: English

L5 ANSWER 52 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

ACCESSION NUMBER: 1992:111738 BIOSIS

DOCUMENT NUMBER: BR42:51738

TITLE: DETECTION OF TRUNCATED AND ALTERNATIVELY SPLICED

TRANSCRIPTS CONTAINING **HER2**-NEU

EXTRACELLULAR DOMAIN IN HUMAN BREAST CANCER CELLS.

AUTHOR(S): ROBLES R; SCOTT G K; TRIPATHY D; PARKS J; SHEPARD H M;

BENZ

C C

CORPORATE SOURCE: CANCER RESEARCH INST., UNIV. CALIFORNIA, SAN FRANCISCO, CALIF. 94143.

SOURCE: 14TH ANNUAL SAN ANTONIO BREAST CANCER SYMPOSIUM, SAN ANTONIO, TEXAS, USA, DECEMBER 6-7, 1991. BREAST CANCER RES TREAT, (1991) 19 (2), 204.

CODEN: BCTRD6. ISSN: 0167-6806.

DOCUMENT TYPE: Conference

FILE SEGMENT: BR; OLD

LANGUAGE: English

L5 ANSWER 53 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1990:345957 BIOSIS
DOCUMENT NUMBER: BR39:41218
TITLE: GROWTH INHIBITION OF HUMAN BREAST CARCINOMA CELLS EXPOSED
TO COMBINATIONS OF INTERFERON-GAMMA AND MONOCLONAL
ANTIBODIES DIRECTED AGAINST THE **EXTRACELLULAR**
DOMAIN OF THE **HER2-ERBB2** ONCOGENE PROTEIN.
AUTHOR(S): KOTTS C E; CARVER M E; CHEN A B
CORPORATE SOURCE: GENENTECH INC., SO. SAN FRANCISCO, CALIF. 94080.
SOURCE: JOINT MEETING OF THE AMERICAN SOCIETY FOR BIOCHEMISTRY AND
MOLECULAR BIOLOGY, AND THE AMERICAN ASSOCIATION OF
IMMUNOLOGISTS, NEW ORLEANS, LOUISIANA, USA, JUNE 4-7,
1990.
FASEB (FED AM SOC EXP BIOL) J, (1990) 4 (7), A1946.
CODEN: FAJOEC. ISSN: 0892-6638.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L5 ANSWER 54 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS
ACCESSION NUMBER: 1991:107492 BIOSIS
DOCUMENT NUMBER: BR40:50312
TITLE: PRODUCTION AND CHARACTERIZATION OF IMMUNOTOXINS TO
DISTINCT
EPITOPES OF THE **EXTRACELLULAR** DOMAIN OF THE
HER-2 GP185.
AUTHOR(S): TECCE R; DI GIESI G; NATALI P G
CORPORATE SOURCE: REGINA ELENA CANCER INST., ROME, ITALY.
SOURCE: THIRD INTERNATIONAL CONFERENCE OF ANTICANCER RESEARCH,
MARATHON, GREECE, OCTOBER 16-20, 1990. ANTICANCER RES,
(1990) 10 (5 PART B), 1454.
CODEN: ANTRD4. ISSN: 0250-7005.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L5 ANSWER 55 OF 59 MEDLINE DUPLICATE 25
ACCESSION NUMBER: 91073143 MEDLINE
DOCUMENT NUMBER: 91073143
TITLE: The **extracellular** domain of **HER2/neu** is
a potential immunogen for active specific immunotherapy of
breast cancer.
AUTHOR: Fendly B M; Kotts C; Vetterlein D; Lewis G D; Winget M;
Carver M E; Watson S R; Sarup J; Saks S; Ullrich A; et al
CORPORATE SOURCE: Genentech, Inc., South San Francisco, CA 94080.
SOURCE: JOURNAL OF BIOLOGICAL RESPONSE MODIFIERS, (1990 Oct) 9 (5)
449-55.
Journal code: JBM. ISSN: 0732-6580.
PUB. COUNTRY: United States
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 199103

AB The proto-oncogene **HER2/neu** encodes a protein tyrosine kinase (p185HER2)
that is homologous to the human epidermal growth factor receptor.
Amplification and/or overexpression of **HER2/neu** occurs in multiple human
malignancies and appears to be integrally involved in progression of some
breast and ovarian cancers. Because of this fact, **HER2/neu** is an
intriguing target for specific cancer therapeutic strategies. One such
strategy is active specific immunotherapy, in which the immune system is
targeted at specific antigens expressed by tumor cells. We have employed
a
transfected cell line that secretes the extracellular domain of p185HER2
as a source of **HER2**-derived immunogen in a guinea pig model. The
immunized

animals develop a cellular immune response, as monitored by delayed-type hypersensitivity, and antisera derived from immunized animals specifically inhibited the in vitro growth of human breast tumor cells overexpressing p185HER2. These data provide support for an immunotherapeutic approach to cancers characterized by overexpression of the HER2/neu proto-oncogene.

L5 ANSWER 56 OF 59 MEDLINE

DUPLICATE 26

ACCESSION NUMBER: 91119659 MEDLINE

DOCUMENT NUMBER: 91119659

TITLE: Differentiation of cultured human breast cancer cells (AU-565 and MCF-7) associated with loss of cell surface HER-2/neu antigen.

AUTHOR: Bacus S S; Kiguchi K; Chin D; King C R; Huberman E

CORPORATE SOURCE: Cell Analysis Systems, Inc., Elmhurst, Illinois.

CONTRACT NUMBER: IR43CA50843-01 (NCI)

SOURCE: ~~MOLECULAR CARCINOGENESIS, (1990) 3 (6) 350-62.~~

Journal code: AEQ. ISSN: 0899-1987.

PUB. COUNTRY: United States

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199105

AB The relationship between terminal cell differentiation and changes in the subcellular levels of the HER-2/neu antigen was investigated in cultured human breast cancer cells: AU-565 cells (which overexpress the HER-2/neu gene) and MCF-7 cells (which do not overexpress this gene). Differentiation was achieved by treating the cells with mycophenolic acid (MPA), phorbol 12-myristate 13-acetate (PMA), retinoic acid (RA), or the TA-1 monoclonal antibody to the **extracellular** domain of the **HER-2/neu** protein. Ten to twenty percent of the cells in untreated, sparsely growing AU-565 cultures exhibited morphological maturation characterized by large lacy nuclei surrounded by sizable flat cytoplasm. A fraction of these cells harbored milk factors such as

casein

and large lipid droplets. Treatment of the AU-565 cells for 4 d with 9 microM MPA, 1.6 nM PMA, 2.5 microM RA, or 1 microgram/mL TA-1 antibody resulted in cell growth inhibition and an increase in the percentage of cells (48-97%) that exhibit a mature phenotype. MCF-7 cells were also susceptible to differentiation by MPA and RA, but to a lesser degree than the AU-565 cells. Differentiation in the AU-565 and MCF-7 cells was associated with reduced immunostaining for the HER-2/neu protein at the cell surface membrane and with a transient increased diffuse immunostaining for this protein in the cytoplasm.

L5 ANSWER 57 OF 59 MEDLINE

DUPLICATE 27

ACCESSION NUMBER: 90361943 MEDLINE

DOCUMENT NUMBER: 90361943

TITLE: ELISA for quantitation of the extracellular domain of p185HER2 in biological fluids.

AUTHOR: Sias P E; Kotts C E; Vetterlein D; Shepard M; Wong W L

CORPORATE SOURCE: Department of Immunology Research and Assay Technologies, Genentech Inc., So. San Francisco, CA 94080.

SOURCE: JOURNAL OF IMMUNOLOGICAL METHODS, (1990 Aug 28) 132 (1) 73-80.

Journal code: IFE. ISSN: 0022-1759.

PUB. COUNTRY: Netherlands

Journal; Article; (JOURNAL ARTICLE)

LANGUAGE: English

FILE SEGMENT: Priority Journals; Cancer Journals

ENTRY MONTH: 199012

AB The HER2/neu proto-oncogene encodes a receptor that belong to the tyrosine-specific protein kinase family. Amplification of the HER2 gene in

patients with breast and ovarian cancer has been shown to predict poorer survival rates. In order to understand the role of HER2 in malignant and normal cells, it is necessary to devise assays that can quantitate expression levels of the HER2 gene product (p185HER2) in production samples, biopsy specimens and biological fluids. We have developed a simple, quantitative ELISA that uses two monoclonal antibodies directed against the **extracellular** domain of the **HER2** gene product, p185HER2 (HER2 ECD). The assay has a detection range of 0.25-120 ng/ml, is precise and sensitive. The ability of this assay to detect biologically active rHER2 ECD is demonstrated by its correlation to a growth inhibitory bioassay ($r = 0.92$). The sandwich ELISA can also accurately quantitate rHER2 ECD in mouse and monkey serum. This assay should be useful for quantitating low levels of circulating rHER2 ECD in animals in which rHER2 ECD is being used as antigen for immunotherapy and in patients which 'shed' receptor.

L5 ANSWER 58 OF 59 BIOSIS COPYRIGHT 2000 BIOSIS

~~ACCESSION NUMBER: 1990:404646 BIOSIS~~
DOCUMENT NUMBER: BR39:75607
TITLE: DIFFERENTIAL GROWTH INHIBITION OF HUMAN CARCINOMA CELLS EXPOSED TO MONOCLONAL ANTIBODIES DIRECTED AGAINST THE **EXTRACELLULAR** DOMAIN OF THE **HER2-ERBB2**.
AUTHOR(S): KOTTS C E; WIRTH C M; CARVER M E; FENDLY B M
CORPORATE SOURCE: GENENTECH INC., DEP. MEDICINAL ANALYTICAL CHEMISTRY, S. SAN FRANCISCO, CALIF. 94080.
SOURCE: FORTY-FIRST ANNUAL MEETING OF THE TISSUE CULTURE ASSOCIATION, HOUSTON, TEXAS, USA, JUNE 10-13, 1990. IN VITRO CELL DEV BIOL, (1990) 26 (3 PART 2), 59A. CODEN: ICDBEO. ISSN: 0883-8364.
DOCUMENT TYPE: Conference
FILE SEGMENT: BR; OLD
LANGUAGE: English

L5 ANSWER 59 OF 59 MEDLINE

DUPLICATE 28

ACCESSION NUMBER: 89231615 MEDLINE
DOCUMENT NUMBER: 89231615
TITLE: HER2 cytoplasmic domain generates normal mitogenic and transforming signals in a chimeric receptor.
AUTHOR: Lee J; Dull T J; Lax I; Schlessinger J; Ullrich A
CORPORATE SOURCE: Department of Developmental Biology, Genentech, Inc., South San Francisco, CA 94080.
SOURCE: EMBO JOURNAL, (1989 Jan) 8 (1) 167-73. Journal code: EMB. ISSN: 0261-4189.
PUB. COUNTRY: ENGLAND: United Kingdom
Journal; Article; (JOURNAL ARTICLE)
LANGUAGE: English
FILE SEGMENT: Priority Journals
ENTRY MONTH: 198908

AB We have investigated the biological function of an unidentified human growth factor, the ligand of the putative HER2 receptor, by characterizing the signalling properties of its receptor. HER2 (or c-erbB-2), the human homolog of the rat neu proto-oncogene, encodes a transmembrane glycoprotein of the tyrosine kinase family that appears to play an important role in human breast carcinoma. Since a potential ligand for HER2 has not yet been identified, it has been difficult to analyze the biochemical properties and biological function of this cell surface protein. For this reason, we replaced the **HER2 extracellular** domain with the closely related ligand binding domain sequences of the epidermal growth factor (EGF) receptor, and examined the ligand-induced biological signalling potential of this chimeric HER1-2 protein. This HER1-2 receptor is targetted to the cell surface of transfected NIH 3T3 cells, forms high and low affinity binding

sites, and genes normal mitogenic and cell transforming signals upon interaction with EGF or TGF alpha. The constitutive activation of wild-type HER2 in transfected NIH 3T3 cells suggests the possibility that these cells synthesize the as yet unidentified HER2 ligand and activate HER2 by an autocrine mechanism.

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COST IN U.S. DOLLARS

SINCE FILE

TOTAL

ENTRY

SESSION

FULL ESTIMATED COST

49.25

49.40

SESSION WILL BE HELD FOR 60 MINUTES

STN INTERNATIONAL SESSION SUSPENDED AT 14:39:18 ON 17 OCT 2000

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L4: Entry 1 of 2

File: USPT

Feb 9, 1999

US-PAT-NO: 5869445

DOCUMENT-IDENTIFIER: US 5869445 A

TITLE: Methods for eliciting or enhancing reactivity to HER-2/neu protein

DATE-ISSUED: February 9, 1999

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cheever; Martin A.	Mercer Island	WA	N/A	N/A
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US-CL-CURRENT: 514/2; 514/21

CLAIMS:

We claim:

1. A method for eliciting or enhancing an immune response to HER-2/neu protein, comprising administering to a human in an amount effective to elicit or enhance said response a polypeptide encoded by a DNA sequence selected from:

(a) nucleotides 2026 through 3765 of SEQ ID NO: 1; and

(b) DNA sequences that hybridize to a nucleotide sequence complementary to nucleotides 2026 through 3765 of SEQ ID NO:1 under moderately stringent conditions, wherein the DNA sequence encodes a polypeptide that produces an immune response to HER-2/neu protein, and wherein the hybridization conditions comprise prewashing in a solution of 5.times.SSC, 0.5% SDS 1.0 mM EDTA (pH 8.0); hybridizing at 50.degree. C.-65.degree. C. 5.times.SSC, overnight; followed by washing twice at 65.degree. C. for 20 minutes with each of 2X, 0.5X and 0.2X SSC, containing 0.1% SDS.

2. The method of claim 1 wherein the polypeptide has the amino acid sequence of SEQ ID NO:2 from lysine, amino acid 676, through valine, amino acid 1255, or a conjugate thereof with a peptide or polypeptide having immunogenic properties.

3. The method of claim 2 wherein the polypeptide has the amino acid sequence of SEQ ID NO:2 from amino acid 676 through amino acid 1255.

4. The method of claim 1 wherein the polypeptide is in combination with a pharmaceutically acceptable carrier or diluent.

WEST**End of Result Set**☐ **Generate Collection**

L4: Entry 2 of 2

File: USPT

Sep 1, 1998

US-PAT-NO: 5801005

DOCUMENT-IDENTIFIER: US 5801005 A

TITLE: Immune reactivity to HER-2/neu protein for diagnosis of malignancies in which the HER-2/neu oncogene is associated

DATE-ISSUED: September 1, 1998

INVENTOR-INFORMATION:

NAME	CITY	STATE	ZIP CODE	COUNTRY
Cheever; Martin A.	Mercer Island	WA	N/A	N/A
Disis; Mary L.	Renton	WA	N/A	N/A

US-CL-CURRENT: 435/7.24; 435/7.1, 435/7.2, 530/300, 530/350

CLAIMS:

We claim:

1. A method of screening for the presence of a malignancy in a warm-blooded animal, wherein a HER-2/neu oncogene is associated with the malignancy, comprising the steps of:
 - (a) obtaining peripheral blood cells from said warm-blooded animal;
 - (b) incubating said cells with HER-2/neu protein; and
 - (c) detecting the presence or absence of specific activation of CD4.sup.+ T cells, wherein the presence of specific activation is indicative of the presence of malignancy.
2. The method of claim 1 wherein a HER-2/neu oncogene is associated with a malignancy selected from the group consisting of breast, ovarian, colon, lung and prostate cancer.
3. The method of claim 1 wherein the step of detecting comprises detecting the presence or absence of proliferation of said T cells.
4. A method for the detection of T cells, from a warm-blooded animal, that recognize HER-2/neu protein, comprising the steps of:
 - (a) obtaining peripheral blood cells from said warm-blooded animal;
 - (b) incubating said cells with HER-2/neu protein; and
 - (c) detecting the presence or absence of specific activation of T cells, wherein the presence of specific activation is indicative of the presence of T cells that recognize HER-2/neu protein.
5. The method of claim 4 wherein step (a) further comprises separating T cells from the peripheral blood cells, and the cells incubated in step (b) are the T cells.

incubated in step (b) are the T cells.

6. The method of claim 4 wherein step (a) further comprises separating CD4.sup.+ T cells or CD8.sup.+ T cells from the peripheral blood cells, and the cells incubated in step (b) are CD4.sup.+ or CD8.sup.+ T cells.

7. The method of any one of claims 4, 5 or 6 wherein the warm-blooded animal is an animal which had been immunized with HER-2/neu peptide prior to step (a).